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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 417 790 A2**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 90117662.8

(22) Date of filing: 13.09.90

(51) Int. Cl.5: C07D 487/14, A61K 31/52, A61K 31/505, //(C07D487/14, 249:00,239:00,235:00)

(30) Priority: 14.09.89 JP 239117/89
06.10.89 JP 261761/89

(43) Date of publication of application:
20.03.91 Bulletin 91/12

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

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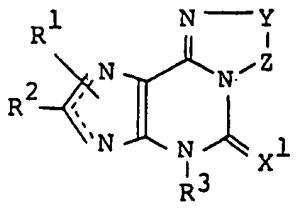
(54) S-triazolo[3,4-i]purine derivatives.

(57) There are disclosed s-triazolo[3,4-i]purine derivatives represented by formula:



wherein Y-Z represents

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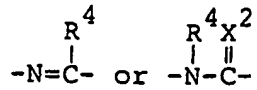


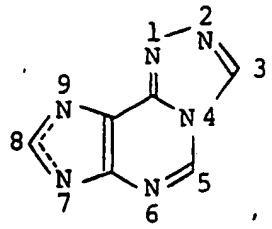
where R^4 represents hydrogen, alkyl, substituted or unsubstituted aromatic heterocyclic group or substituted or unsubstituted aryl; and X^2 represents oxygen, sulfur or NH; each of R^1 and R^2 independently represents hydrogen, alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl; R^3 represents alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl; X^1 represents oxygen or sulfur; and

represents a single bond or a double bond or pharmaceutically acceptable salts thereof.

S-TRIAZOLO[3,4-i]PURINE DERIVATIVES

The present invention relates to novel s-triazolo[3,4-i]purine derivatives which possess a broncho-dilatory activity, diuretic activity, renal protecting activity and/or anti-amnestic activity.

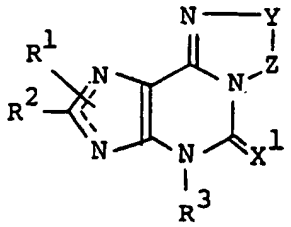
As s-triazolo[3,4-i]purine derivatives represented by the following formula :



9H-s-triazolo[3,4-i]purine which has no substituents at the 3-, 5-, 7- and 8-positions and s-triazolo[3,4-i]-purine derivatives which have benzyl at the 7- or 9-position are disclosed in J. Org. Chem., 30 , 3601 (1965); and 3-alkylthio-s-triazolo[3,4-i]purine having SH, SCH_3 or SCH_2CONH_2 at the 3-position is disclosed in Aust. J. Chem., 35 , 1263 (1982). As yet their pharmacological activities are unknown. Furthermore, s-triazolo[3,4-i]purine derivatives having a substituent at the 5-position thereof have not been reported so far.

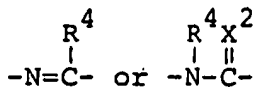
An object of the present invention is to provide novel s-triazolo[3,4-i]purine derivatives having an broncho-dilatory effect, anti-asthmatic effect, diuretic effect, renal protecting effect and/or anti-amnestic effect.

The present invention is directed to s-triazolo[3,4-i]purine derivatives represented by formula (I):



(I)

wherein Y-Z represents



where R^4 represents hydrogen, alkyl, a substituted or unsubstituted aromatic heterocyclic group or substituted or unsubstituted aryl; and X^2 represents oxygen, sulfur or NH;

each of R^1 and R^2 independently represents hydrogen, alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl;

R^3 represents alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl;

X^1 represents oxygen or sulfur;

and

represents a single bond or a double bond or pharmaceutically acceptable salts thereof.

In the definitions of the groups in formula (I), the alkyl means a straight or branched alkyl having 1 to 10 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl,

neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc. The cycloalkyl includes an alicyclic alkyl having 3 to 8 carbon atoms such as cyclopropyl,cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, etc. The aralkyl includes aralkyls having 7 to 15 carbon atoms such as benzyl, phenethyl, benzhydryl, etc. The aryl includes aryls having 6 to 10 carbon atoms such as phenyl, naphthyl, etc. The substituent in the substituted aryl includes one or two of the same or different lower alkyl, trifluoromethyl, hydroxyl, lower alkoxyl, lower alkylthio, nitro, halogen, amino, lower alkylamino, lower alkanoylamino, aroylamino, carboxyl, lower alkoxycarbonyl, lower alkanoyl and aroyl, etc. The aromatic heterocyclic group includes heterocyclic rings of 5- or 6-members such as thienyl, furyl, pyrazolyl, oxazolyl, imidazolyl, pyridyl, etc. The substituent in the substituted heterocyclic group includes one or two of the same or different lower alkyl, lower alkoxyl, halogen, etc.

The lower alkyl and the alkyl moiety in the lower alkoxyl, lower alkylthio, lower alkylamino and lower alkoxycarbonyl means a straight or branched alkyl having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, etc.

The lower alkanoyl and the alkanoyl moiety in the lower alkanoylamino include alkanoyl having 1 to 6 carbaon atoms such as formyl, acetyl, propionyl, butyryl, isobutyl, pivaloyl, valeryl, isovaleryl, etc.

The aroyl and the aroyl moiety in the aroylamino include, for example, benzoyl, toluyl, propylbenzoyl, naphthoyl, etc.

The halogen means fluorine, chlorine, bromine and iodine.

The salts of Compound (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, amino acid addition salts, etc.

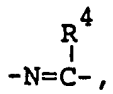
The pharmaceutically acceptable acid addition salts of Compound (I), include inorganic acid salt such as hydrochloride, sulfate, phosphate, etc. and organic acid salts such as acetate, maleate, fumarate, tartarate, citrate, etc. The pharmaceutically acceptable metal salts include alkali metal salts such as sodium salt, potassium salt etc.; alkaline earth metal salts such as magnesium salt, calcium salt, etc. and further an aluminum salt and a zinc salt. The pharmaceutically acceptable organic amine addition salts include addition salt of morpholine, piperidine, etc. The pharmaceutically acceptable amino acid addition salts, include lysine, glycine, phenylalanine, etc.

The methods for preparing Compound (I) are described below.

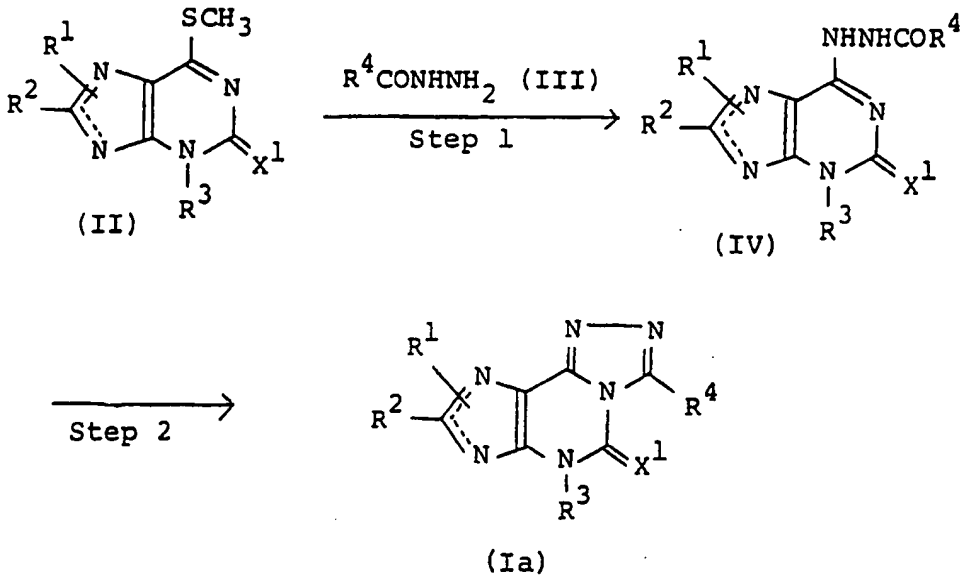
When the defined groups are changed under the conditions of the following processes or are inadequate to proceeding of the following processes, processes can be readily carried out by a usual method in the organic synthetic chemistry, for example, by protection of functional groups, elimination of protecting groups.

Process 1

Compound (Ia), which is Compound (I) where Y-Z is



is synthesized according to Steps 1 and 2.



wherein X^1, R^1, R^2, R^3 and R^4 have the same significance as described above.

(Step 1)

Compound (IV) is obtained by reacting Compound (II) with Compound (III).

Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; ketones such as acetone, methyl ethyl ketone, etc.; aromatic hydrocarbons such as toluene, xylene, etc.; halogenated hydrocarbons such as dichloroethane, 1,1,2,2-tetrachloroethane, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination. The reaction is performed at 50 to 200° C and completed in 10 minutes to 72 hours.

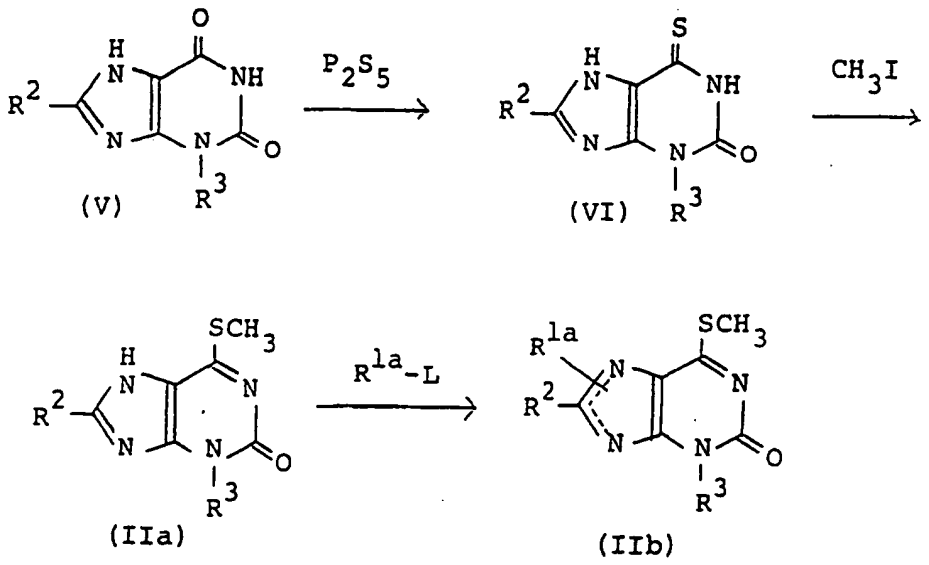
(Step 2)

Compound (Ia) is obtained by cyclization of Compound (IV). The reaction is performed in a solvent in the presence of an acid catalyst.

The acid catalyst includes, for example, hydrochloric acid, sulfuric acid, sulfonic acid such as p-toluenesulfonic acid, camphor sulfonic acid, etc., or silica gel powders. The acid catalyst is used alone or in combination.

Any solvent is used so long as it is inert to the reaction. The solvent includes aromatic hydrocarbons such as toluene, xylene, etc.; halogenated hydrocarbons such as dichloroethane, 1,1,2,2-tetrachloroethane, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination. The reaction is performed at 50 to 150° C and completed in 10 minutes to 4 hours.

Compounds (IIa) and (IIb), among the starting Compound (II) wherein X^1 is oxygen is prepared by the method of Kleiner et al. [J. Chem. Soc., Perkin I, 739 (1973)] or by a modified method of Kleiner et al. The reaction steps are illustrated as follows.



wherein R^{1a} represents a group other than hydrogen in the definition for R^1 described above; R^2 and R^3 have the same significance as described above; and L represents a leaving group.

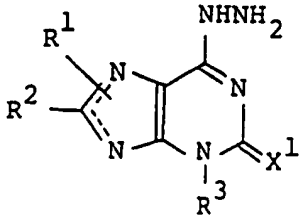
The leaving group denoted by L includes, for example, halogen atom such as chlorine, bromine, iodine, etc.; alkylsulfonyloxy such as methanesulfonyloxy, etc.; arylsulfonyloxy such as phenylsulfonyloxy, p-toluenesulfonyloxy, etc.

Compound (V) in step 2 is synthesized by a notorious method [Biochemistry, 16 , 3316 (1977)] or its modified method.

The starting Compound (IIC), which is Compound (II) where X^1 is sulfur is synthesized by the method of Jacobson et al. [J. Med. Chem., 32 , 1873 (1989)] or by a modified method of Jacobson et al.

Process 2

Compound (Ia) is also synthesized by reacting Compound (VII) with Compound (VIII). The reaction is performed in the presence or absence of solvent.



(VII)

(wherein X^1, R^1, R^2 and R^3 have the same significance as described above.)

$R^4C(OR^5)_3$ (VIII)

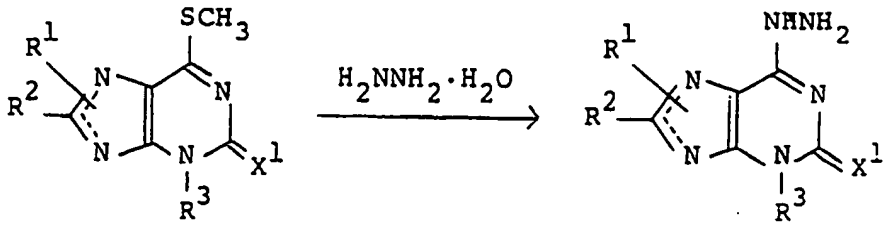
(wherein R^4 has the same significance as described above and R^5 represents alkyl having 1 to 10 carbon atoms.)

Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, ethers such as tetrahydrofuran, dioxane, etc.; dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; alcohols such as methanol, ethanol, isopropyl alcohol, etc.; halogenated hydrocarbons such as dichloroethane, 1,1,2,2-tetrachloroethane, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination.

The reaction is performed at 50 to 150° C and completed in 10 minutes to 4 hours.

The starting Compound (VII) is prepared from Compound (II) according to a modification of the

notorious method as described in Il Farmaco Ed. Sci., 40 , 221 (1985). The reaction is performed as follows.

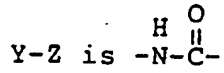


(II) (VII)

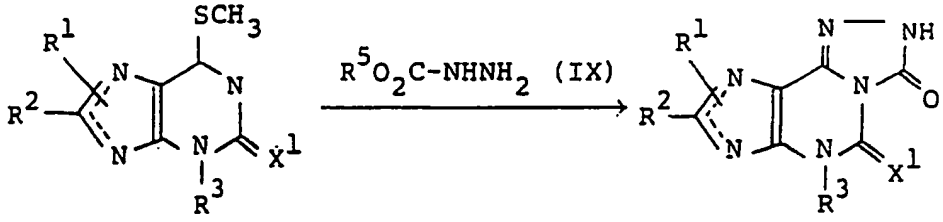
(wherein X^1, R^1, R^2 and R^3 have the same significance as described above.)

Process 3

Compound (Ib1) which is Compound (I) wherein



is synthesized according to the following step.



(II) (Ib1)

(wherein R^1, R^2, R^3, R^5 and X^1 have the same significance as described above.)

Compound (Ib1) is obtained by reacting Compound (II) with Compound (IX).

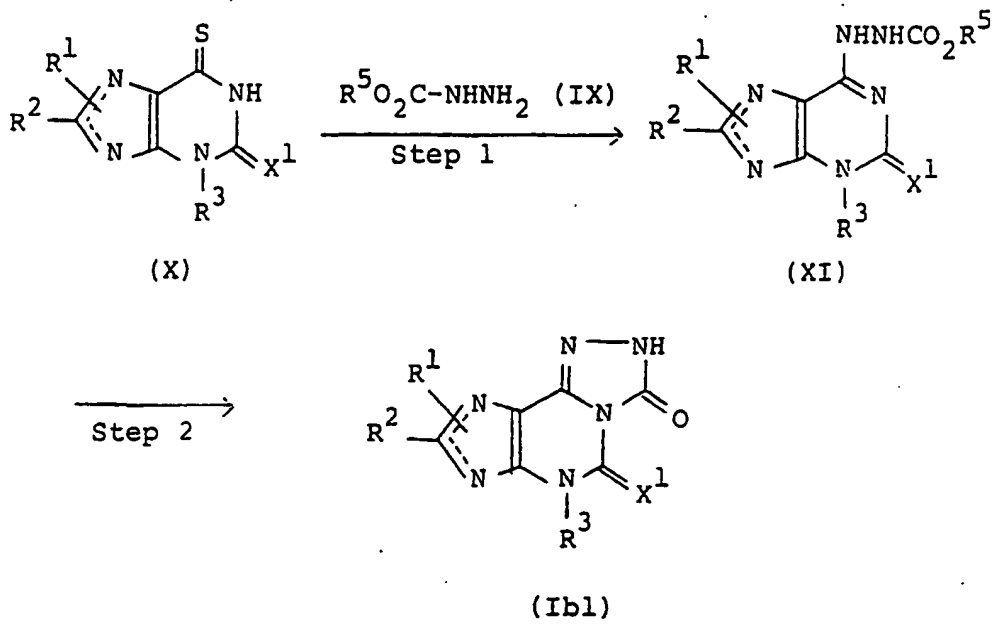
Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; ketones such as acetone, methyl ethyl ketone, etc.; aromatic hydrocarbons such as toluene, xylene, etc.; halogenated hydrocarbons such as dichloroethane, 1,1,2,2-tetrachloroethane, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination. The reaction is performed at 50 to 200° C and completed in 10 minutes to 12 hours.

The starting Compound (II) is obtained by the process shown in Process 1.

The starting Compound (IX) is commercially available.

Process 4

Compound (Ib1) is also synthesized by the following steps:



(X) (XI) (Ibl)

(wherein R^1, R^2, R^3, R^5 and X^1 have the same significance as described above.)

(Step 1)

Compound (XI) is obtained by reacting Compound (X) with Compound (IX).

Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; alcohols such as methanol, ethanol, n-butanol, etc.; ketones such as acetone, methyl ethyl ketone, etc.; aromatic hydrocarbons such as toluene, xylene, etc.; halogenated hydrocarbons such as dichloroethane, 1,1,2,2-tetrachloroethane, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination.

The reaction is carried out at 50 to 200° C and completed in 1 to 48 hours.

The starting Compound (Xa), which is Compound (X) wherein X^1 is oxygen can be prepared by the method of Reichman et al. [J. Chem. Soc., Perkin I, 2647 (1973)] or, by the method of Woodridge et al. [J. Chem. Soc., 1863 (1962)] or by a modification of these methods.

The starting Compound (Xb), which is Compound (X) wherein X^1 is sulfur can be prepared by the method of Jacobson et al. [J. Med. Chem., 32 , 1873 (1989)] or by a modified method of Jacobson et al.

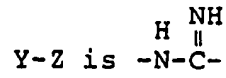
(Step 2)

Compound (Ib1) is obtained by cyclization of Compound (XI). The reaction is performed under heating in the presence or absence of a solvent. Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; alcohols such as methanol, ethanol, n-butanol, etc.; dimethylsulfoxide, etc. The solvent is used alone or is combination.

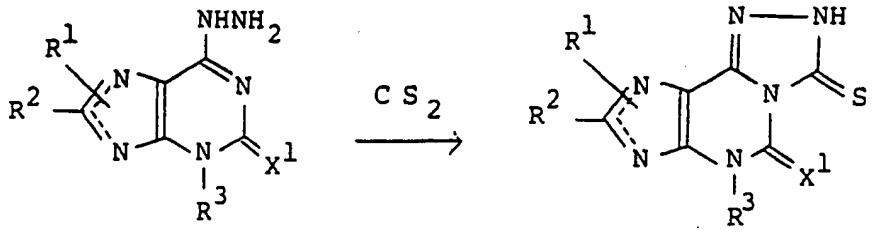
The reaction is carried out at 100 to 200° C and completed in 1 to 24 hours.

Process 5

Compound (Ib2) which is Compound (I) wherein

Y-Z is 

is synthesized by the following step.



(VII) (Ib2)

(wherein R^1, R^2, R^3 and X^1 have the same significance as described above.)

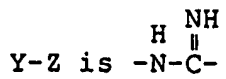
Compound (Ib2) can be synthesized by reacting Compound (VII) with carbon disulfide in the presence of or absence of a solvent. Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, pyridines such as pyridine, quinoline, etc.; dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination.

The reaction is performed at 50 to 200° C and completed in 10 minutes to 5 hours.

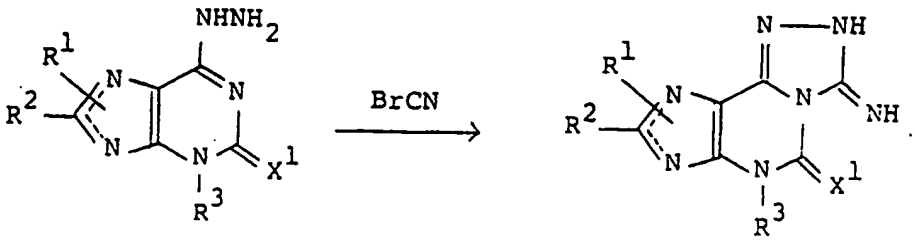
The starting Compound (VII) is obtained by the process shown in Process 2.

Process 6

Compound (Ib3), which is Compound (I) wherein

Y-Z is 

is synthesized by the following step.



(VII) (Ib3)

(wherein R^1, R^2, R^3 and X^1 have the same significance as described above.)

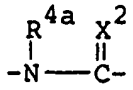
Compound (Ib3) can be synthesized by reacting Compound (VII) with cyanogen bromide.

Any solvent is used so long as it is inert to the reaction. The solvent includes, for example alcohols such as methanol, ethanol, etc.; ethers such as dioxane, tetrahydrofuran, etc., aliphatic nitriles such as acetonitrile, propionitrile, etc.; dimethylalkanamides such as dimethylformamide, dimethylacetamides etc. The solvent is used alone or in combination.

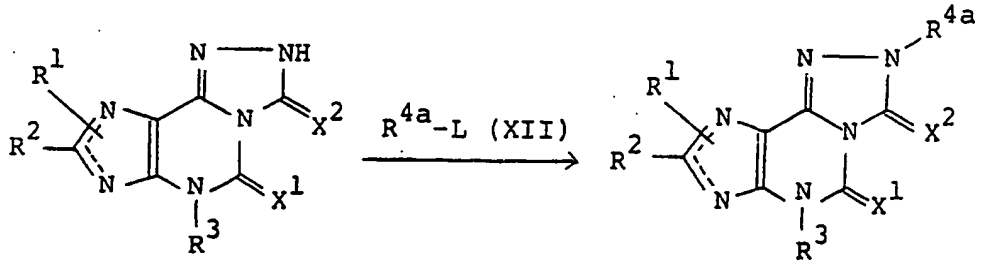
The reaction is performed at 50 to 200° C and completed in 10 minutes to 5 hours.

Process 7

Compound (Ib4) which is Compound (I) wherein Y-Z is



is obtained by the following step.



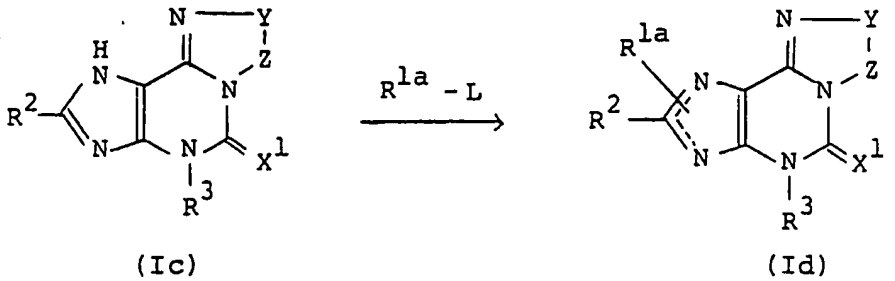
(Ib1), (Ib2), (Ib3) (Ib4)

(wherein R^1, R^2, R^3, X^1 and X^2 have the same significance as described above, and R^{4a} represents a group other than hydrogen in the definition of R^4 described above.)

Compound (Ib4) can be synthesized by reacting Compound (Ib1), (Ib2) or (Ib3) with Compound (XII) in a solvent. The reaction is performed preferably in the presence of a base. Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, ethers such as tetrahydrofuran, dioxane,etc., dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc; alcohols such as methanol, ethanol, isopropyl alcohol, etc.; or dimethylsulfoxide, etc. The solvent is used alone or in combination. The base includes alkali metal carbonates such as potassium carbonate, sodium carbonate, etc.; hydrated alkali metals such as sodium hydride, potassium hydride, etc.; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, etc. The reaction is performed at 0 to 150 °C and completed in 10 minutes to 12 hours.

Process 8

Compound (Id), which is Compound (I) wherein R^{1a} represents a group other than hydrogen in the definition of R^1 is obtained by the following step.



(Ic) (Id)

(wherein R^{1a} represents a group other than hydrogen in the definition of R^1 described above and, X^1, R^2, R^3 and L have the same significance as described above.)

Compound (Id) can be synthesized by reacting Compound (Ic), which is Compound (I) wherein R^1 is hydrogen, with R^{1a}-L, preferably in the presence of a base.

Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, ethers such

as tetrahydrofuran, dloxane,etc., dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; alcohols such as methanol, ethanol, isopropyl alcohol, etc.; or dimethylsulfoxide, etc. The solvent is used alone or in combination. The base includes alkali metal carbonates such as potassium carbonate, sodium carbonate, etc.; hydrated alkali metals such as sodium hydride, potassium hydride, etc.; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, etc.

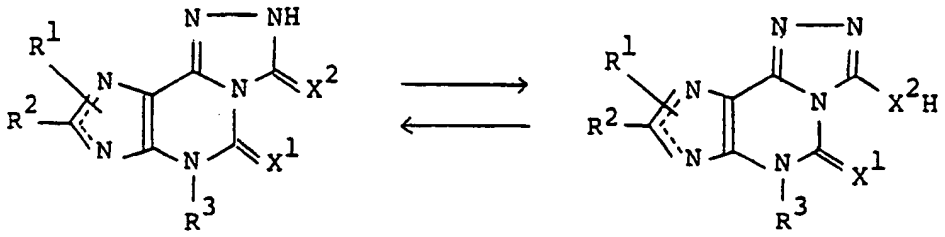
The reaction is performed at 0 to 150° C and completed in 10 minutes to 12 hours.

The intermediates and objective compounds in the respective methods described above is isolated and purified by purification methods conventionally used in organic synthetic chemistry, for example, filtration, extraction, drying, concentration, recrystallization, various column chromatographies, etc. The intermediates can be directly used in the subsequent reaction, without any particular purification.

In the case that it is desired to obtain salts of Compound (I), when Compound (I) is obtained in the form of its salt, Compound (I) is purified as it is. When Compound (I) is obtained in the free form, its salts are formed in a conventional manner, for example, Compound (I) is suspended or dissolved in an appropriate solvent, and an acid or base is added to the solution or suspension.

Furthermore, Compound (I) and pharmaceutically acceptable salts thereof may exist in the form of addition products to water or various solvents; in this case, the pharmaceutically acceptable salts are also included in the present invention.

Furthermore, Compounds (Ib1), (Ib2) and (Ib3) wherein R^4 is hydrogen may be present in the form of Compound (Ibt) as tautomers.

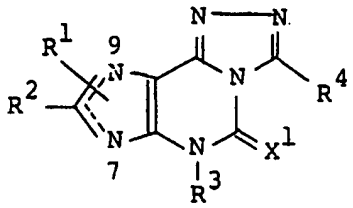


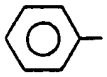
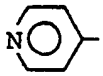
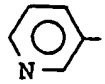
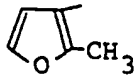
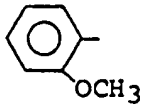
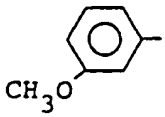
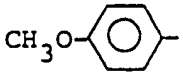
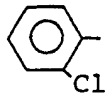
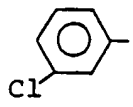
(Ib1), (Ib2), (Ib3) (Ibt)

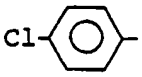
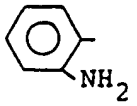
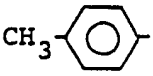
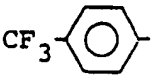
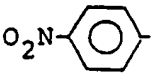
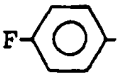
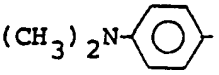
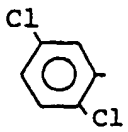
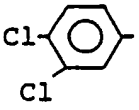
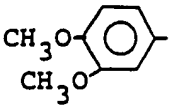
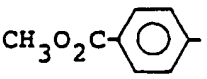
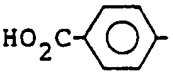
All the possible stereoisomers including the tautomers and mixtures are also included in the scope of the present invention.

Specific examples of Compound (I) obtained by the various methods are shown in Table 1.

Table 1-1



Compound No.	R^1	R^2	R^3	R^4	X^1
1	9-CH_3	H	$(CH_2)_2CH_3$		O
2	9-CH_3	H	$(CH_2)_2CH_3$		O
3	9-CH_3	H	$(CH_2)_2CH_3$		O
4	9-CH_3	H	$(CH_2)_2CH_3$		O
5	9-CH_3	H	$(CH_2)_2CH_3$		O
6	9-CH_3	H	$(CH_2)_2CH_3$		O
7	9-CH_3	H	$(CH_2)_2CH_3$		O
8	9-CH_3	H	$(CH_2)_2CH_3$		O
9	9-CH_3	H	$(CH_2)_2CH_3$		O
10	9-CH_3	H	$(CH_2)_2CH_3$		O
11	9-CH_3	H	$(CH_2)_2CH_3$		O

Compound No.	R^1	R^2	R^3	R^4	X^1
12	9-CH_3	H	$(CH_2)_2CH_3$		O
13	9-CH_3	H	$(CH_2)_2CH_3$		O
14	9-CH_3	H	$(CH_2)_2CH_3$		O
15	9-CH_3	H	$(CH_2)_2CH_3$		O
16	9-CH_3	H	$(CH_2)_2CH_3$		O
17	9-CH_3	H	$(CH_2)_2CH_3$		O
18	9-CH_3	H	$(CH_2)_2CH_3$		O
19	9-CH_3	H	$(CH_2)_2CH_3$		O
20	9-CH_3	H	$(CH_2)_2CH_3$		O
21	9-CH_3	H	$(CH_2)_2CH_3$		O
22	9-CH_3	H	$(CH_2)_2CH_3$		O
23	9-CH_3	H	$(CH_2)_2CH_3$		O
24	9-CH_3	H	$(CH_2)_2CH_3$	CH_3	O
25	H	H	$(CH_2)_2CH_3$	CH_3	O

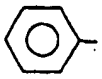
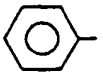
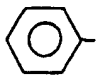
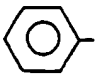
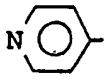
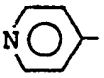
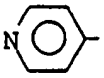
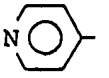
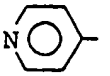
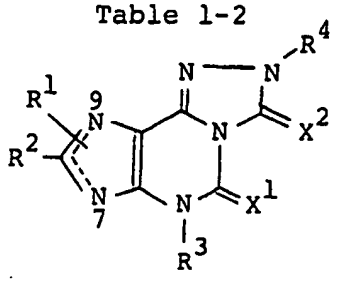
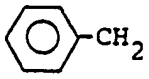
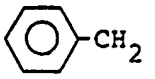
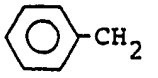
Compound No.	R^1	R^2	R^3	R^4	X^1
26	H		$(CH_2)_2CH_3$		O
27	H		$(CH_2)_2CH_3$	CH_3	O
28	9-CH_3	H	-CH_2- 		O
29	9-CH_3	H			O
30	H	H	$(CH_2)_2CH_3$		O
31	H	H	$(CH_2)_2CH_3$		O
32	H	H	$(CH_2)_2CH_3$		O
33	H	H	$(CH_2)_2CH_3$		O
34	H	H	-CH_2- 		O
35	9-$(CH_2)_2CH_3$	H	$(CH_2)_2CH_3$		O
36	9-CH_3	H	$(CH_2)_2CH_3$	H	O
37	9-CH_3	H	-CH_2- 	CH_3	O
38	H	H	$(CH_2)_3CH_3$		O
39	9-CH_2- 	H	$(CH_2)_2CH_3$		O
40	9-$(CH_2)_2CH_3$	H	$(CH_2)_2CH_3$		O

Table 1-2



Compound No.	R^1	R^2	R^3	X^1	X^2	R^4
41	9-CH_3	H	$CH_3(CH_2)_2$	O	O	H
42	9-CH_3	H		O	O	H
43	H		$CH_3(CH_2)_2$	O	O	H
44	9-$(CH_2)_2CH_3$	H	$CH_3(CH_2)_2$	O	O	H
45	H	H	$CH_3(CH_2)_2$	O	O	H
46	9-CH_3	H	$CH_3(CH_2)_2$	O	S	H
47	9-CH_3	H		O	S	H
48	9-CH_3	H	$CH_3(CH_2)_2$	O	O	C_2H_5
49	9-CH_3	H		O	O	C_2H_5
50	9-CH_3	H	$CH_3(CH_2)_2$	O	NH	H
51	9-CH_3	H	$CH_3(CH_2)_3$	O	O	H

The pharmacological activities of Compound (I) represented by the general formula (I) are illustrated as follows.

(a) Effects on passive Schultz-Dale reaction (bronchodilatory effects)

Guinea pigs were passively sensitized as follows. Hartley male guinea pigs weighing 350 to 500 g were

injected intraperitoneally with rabbit anti-egg albumin (EWA) serum prepared by the method of Koda et al. [Folia pharmacol., Japon 66 , 237, (1970)]. After 24 hours, the guinea pigs were stunned and exsanguinated, and then trachea was excised. The zig-zag strips of the trachea were prepared by the method of Emmerson and Mackay [J. Pharm. Pharmacol., 31 , 798, (1979)]. The strips were suspended in Krebs-Henseleit solution at 37° C under aeration of a mixed gas of 95% oxygen and 5% carbon dioxide, and incubated for one hour. Antigen (EWA) was then introduced in the solution (final concentration; 1 µg/ml), and the contraction was measured by isotonictrasducer (TD-112s, made by Nihon Kohden K.K., Japan) and recorded on a recorder (Type 3066, made by Yokogawa-Hokushin Denki, K.K. Japan). After the contraction curves reached plateau the compounds were successively added in order to get cumulative concentration-relaxation curves. Concentration of 50% relaxation rate (IC_{50}) was calculated from the regression line, which was obtained from cumulative concentration-relaxation curves.

The results are shown in Table 2.

(b) Effects on experimental asthma

Guinea pigs were passively sensitized as follows. Hartley male guinea pigs weighing 350 to 500 g were intraperitoneally injected with 1 ml of rabbit anti-egg alubmin (EWA) serum prepared by the method of Koda et al. [Folia pharmacol., Japon, 66 , 237 (1970)]. The animals were treated with intraperitoneal injection of diphenhydramine (20 mg/kg) and propranolol (5 mg/kg), 30 minutes before administration of test compounds. 17 hours after the sensitization, the test compounds (50 mg/kg or 5 mg/kg) or saline (control) were orally administrated to sensitized animals. After one hour from the administration of the test compounds, the guinea pigs were placed in plastic observation box and were exposed to an aerosal antigen of 1.5% EWA.

The time until the onset of respiratory distress-like symptom [collapse time (second)] was measured as a result of experimental asthma.

The results are shown in Table 2.

(c) Inhibition effect on platelet activating factor (PAF)-induced mortality

The experiment was performed by a minor modification of method of Carlson et al. [Agents and Actions, 21 , 379 (1987)]. Groups each consisting of 10 male dd mice (weighing 28 to 32 g) were used, and 100 mg/kg of test compound or a saline (control) was orally administrated. One hour after the administration of test compound, 40 µg/kg of PAF (manufactured by Avanti Polar Lipids Co., Ltd.) was intravenously administered. Two hours after PAF injection, the mortality rate of the animals was observed. The compound whose mortality rate was significantly ($p < 0.05$: Fischer's accurate probability tests) lower than control is regarded as having inhibitory effect on PAF-induced mortality, and the results in Table 2 were represented by minimum effective dose (MED).

Table 2

Compound	Passive Schultz-Dale reaction IC_{50} (μM)	Experimental asthma Collapse time (sec) n = 3-10 means±S.E.M.	PAF-induced mortality MED (mg/kg)
1	4.1		
2	0.40		
3	0.032	422 ± 130	
4	7.7	358 ± 65	
5	0.70		100
6			100
8	5.6		
9	7.8		
10	18		
11	>40		100
12	26	399 ± 55**	100
14	45		
24			100
25	0.42	590 ± 9.8	100
30	0.76		10
31	11	512 ± 52	25
38	>40	401 ± 78	25
44	39.6		
Theophylline*	23	414 ± 47	100
Control		254 ± 18	

* The Merck Index 11th 9212 (1989)

** Administration dose of Compound 12 was 5 mg.kg (Administration dose of the other compounds were 50 mg.kg)

(d) Diuretic activity

Wistar male rats weighing 150 to 300 g were used after fasting for 18 hours. A test compound or saline (control) was orally administered to rats (dose: 25 mg/kg) and urine was taken for 6 hours. The test was performed using 3 groups per test compound, and each group consists of 3 animals. The urine was metered by a measuring cylinder and electrolytes (Na^+ and K^+) in the urine were analyzed by flame photometer (model 775A: Hitachi Ltd.).

The results are shown in Table 3.

Parameters in Table 3 are represented by relative value for control.

Table 3

Compound	Urine volume (%)	Excretion of Na^+ (%)	Excretion of K^+ (%)	Na^+/K^+
Control	100	100	100	1.00
1	255	226	87	3.18
3	274	224	196	1.09
4	177	167	134	1.25
6	223	240	146	1.64
7	173	162	122	1.33
8	170	175	122	1.44
9	253	219	139	1.57
10	162	134	109	1.24
11	255	302	134	2.26
12	198	183	129	1.42
16	170	194	175	1.11
17	178	179	134	1.42
18	155	141	129	1.09
24	160	148	168	1.23
25	161	193	119	1.63
29	170	155	110	1.41
30	204	220	124	1.77
31	191	196	118	1.66
38	353	293	180	1.63
32	195	196	129	1.52
39	185	184	145	1.27
40Sa*	155	132	136	0.97
44	191	142	128	1.11
49	300	279	173	1.61
51	200	152	152	1.00
Furosemide**	175	164	157	1.05

* 40Sa is hydrochloride salt of Compound 40.
** The Merck Index 11th 4221 (1989).

(e) Effect on renal protecting activity (glycerol-induced renal deficient model):

Renal insufficiency is the condition that homeostasis of body fluid failed to maintain by disorder of renal function. It is well known that subcutaneous or intramuscular administration of glycerol to rat induce acute renal insufficiency characterized by renal tubular disturbance [Can J. Physiol. Pharmacol., 65 42 (1987)].

Wistar male rats (fasted both food and water for 18 hours) were used. A test compound or saline (control) was intraperitoneally administered (dose: 0.1 ml/100 g) to rats. After 30 minutes rats were anesthesized with ether and the back skin was picked up and 0.8 ml /100 g of 50% glycerol was subcutaneously administered. 24 hours after the glycerol injection, the rats were anesthesized with ether and 5 ml of the blood was collected from the descending aorta. To obtain the serum, after allowing it to stand for 30 minutes or longer, the blood sample was centrifuged at 3000 rpm for 10 minutes. Creatinine in the serum sample was determined using autoanalyzer (AU510, Olympus) or clinical analysis kit of creatinine (Creatinine Test Wako; by Wako Pure Chemical Ind., Japan). Urea nitrogen in the serum was determined using autoanalyzer (AU510; made by Olympus Optical Co., Ltd, Japan) or clinical analysis kit of urea nitrogen (Urea nitrogen test wako; by Wako Pure Chemical Ind., Japan).

The results are shown in Table 4.

Further, the left kidneys of test compound-treated groups and control groups were taken out from the animals and the kidneys were prepared for pathological sample.

As the result of patholozic autopsy for kidneys, it was indicated that the renal insufficiency was

improved by the test compounds as shown in Table 4.

Table 4

Compound No.	Creatinine in serum (mg/dl)		Urea nitrogen in serum (mg/dl)	
	Glycerol treated		Glycerol treated	
	Control	Test compound administrated (Significance for control*)	Control	Test compound administrated (Significance for control*)
3	2.64±0.27	1.90±0.15 (p<0.05)		
4	2.64±0.27	1.80±0.11 (p<0.05)		
6	4.76±0.18	2.76±0.27 (p<0.001)	171.1±7.7	100.8±9.3 (p<0.001)
7	4.06±0.30	2.96±0.30 (p<0.05)	143.4±8.1	119.9±11.3 (p<0.05)
8	4.09±0.29	1.97±0.23(p<0.001)	137.9±7.2	76.4±9.6 (p<0.001)
10	5.01±0.19	2.81±0.33 (p<0.001)		
11	4.09±0.29	2.22±0.16 (p<0.001)	137.9+7.2	91.1±7.8 (p<0.001)
14	4.09±0.29	2.91±0.41 (p<0.05)	137.9±7.2	115.9±16.5 N.S.
19	4.06+0.30	2.73±0.38 (p<0.05)	143.4±8.1	99.1±12.7 (p<0.01)
20	3.17±0.28	1.89±0.33 (p<0.001)	131.9±9.0	70.9±17.1 (p<0.01)
28	5.01±0.19	2.68±0.35 (p<0.001)		
31	5.01±0.19	3.05±0.31 (p<0.001)		
42	3.17±0.28	2.19±0.14 (p<0.01)	131.9±9.0	81.4±9.6 (p<0.01)
44	3.17±0.28	2.10±0.20 (p<0.01)	131.9±9.0	75.9±17.2 (p<0.01)
Aminophylline**	2.03±0.18	1.72±0.07 N.S.	46.2±6.5	30.6±2.0 (P<0.05)
Furocemide***	3.22±0.35	4.17±0.41 N.S.	110.7±9.4	150.3±13.7 (p<0.05)
Normal control	Glycerol untreated 0.50±0.02		Glycerol untreated 15.2±0.9	

* Student-t test was used for level of significance
** The Merck Index 11th 477 (1989)
*** The Merck Index 11th 4221 (1989)
N.S. No significant difference

(f) Effect on electroconvulsive shock (ECS)-induced amnesia:

Male ddy mice (weighing 23 to 29 g) were used and each group consists of 14 to 15 animals. These tests were performed with a step through type passive avoidance apparatus. As experimental apparatus, two rooms (bright and dark) with automatic management system were used. An experimental apparatus is composed of a bright room equipped with 4W of fluorescent light (15 x 9 x 11 cm) and a dark room (15 x 14 x 18 cm), the two rooms are separated by a guillotine door of 3 x 3 cm. The floor of both rooms is stainless steal grid floor and the weak electric current can be send the grid floor of dark room. In the automatic management system, latency of acquisition trial and test trial are measured automatically by controlling with a controller (TK-402, by UNICOM, Japan).

The test compound was dissolved in saline and saline was used as a control. The test compound and the saline (control) were orally administered 60 minutes before the acquisition trial, respectively.

Acquisition trial for learning was performed as follows. An animal placed in the bright room could enter, through the door into the dark room that had a grid on the floor. As soon as the mouse entered the dark room, a scrambled foot-shock (0.18 mA) was delivered to the floor grid for 2 seconds. In the test trial, given 24 hours after the acquisition trial, the animal was again placed in the bright room and the response latency to enter the dark room was measured. The mice which required over 60 seconds to move from the bright room into the dark room were excluded from the test trial. Immediately after the acquisition trial, electric convulsive shock (ECS) (25 mA, 0.2 second, 2000 V) was loaded on mice. The test trial was performed 24 hours after the ECS treatment as follows. The mice received the acquisition trial were placed in the bright room and, latency from the door opening to the entrance of the whole body of animal into the dark room was measured. The maximum measurement time was 600 seconds and latency exceeding 600 seconds

was recorded as 600 seconds.

The results are shown in Table 5.

Statistical significance between the control group and test compound treated group was judged by Man Whitney U-test.

Table 5

Test Compound	Dose of test compound (mg/kg)	ECS treatment	Number of animals	Latency of test trial	
				(Sec) mean ±S.E.M.	Comparison of test compound with control
Normal	0	-	15	529.3±26.1	
Control	0	+	30	70.9±13.5	p<0.001*
Compound 41	0.625	+	15	105.9±44.0	No significance
	2.5	+	15	111.3±20.1	p<0.05
	10	+	15	97.4±38.7	No significance
	40	+	15	171.8±43.1	p<0.01

* Comparison of control with normal

(g) Effect on scopolamine-induced amnesia:

Acquisition trial was performed in a manner similar to Experiment (f). Amnestic treatment was performed by intraperitoneal administration of scopolamine (0.5 mg/kg), 30 minutes prior to the acquisition trial. The test trial was performed 24 hours after the acquisition trial and its latency was determined as in Experiment (f).

Preparation of administrated test compound was performed in a manner similar to Experiment (f). Test compound and the saline were orally administered 60 minutes before the acquisition trial, respectively.

The results are shown in Table 6.

Table 6

Test Compound	Dose of test compound (mg/kg)	Scopolamine treatment	Number of animals	Latency of test trial	
				(Sec) mean ±S.E.M.	Comparison of test compound with control
Normal	0	-	30	582.6±11.1	
Control	0	+	30	40.9± 8.1	p<0.001*
Compound 41	0.625	+	30	96.8±21.5	p<0.01
	2.5	+	30	115.8±26.6	p<0.01
	10	+	30	53.4± 8.9	p<0.05
	40	+	30	74.3±18.8	No significance
Control	0	+	45	37.0± 6.2	p<0.001*
Compound 51	0.625	+	15	37.0±11.2	No significance
	2.5	+	15	69.5±16.6	p<0.01
	10	+	15	139.9±45.1	p<0.001
	40	+	15	166.3±49.9	p<0.0001

* Comparison of control with normal

(h) Acute toxicity

The compounds were orally administrated to male dd-mice weighing 20 ± 1 g. Minimum lethal dose (MLD) was determined by observing the mortality for seven days after the administration.

The results are shown in Table 7.

Table 7

Compound No.	MLD (mg/kg)	Compound No.	MLD (mg/kg)	Compound No.	MLD (mg/kg)
1	100	22	>300	41	>300
2	300	23	>300	42	>300
3	100	24	300	43	>300
4	200	25	100	44	>300
5	>300	26	>300	46	>300
6	200	27	>300	48	>300
7	300	28	>300	51	>300
8	>300	29	>300		
9	>300	30	300		
10	300	31	>300		
11	>300	33	>300		
12	>300	36	300		
13	>300	37	>300		
14	>300	38	>300		
15	>300	39	>300		
16	>300	40Sa*	100		
17	>300				
18	>300				
19	>300				
20	>300				
21	>300				

* 40Sa is hydrochloride of Compound 40.

Compounds (I) or their pharmaceutically acceptable salts are used directly or in various dosage forms. In the present invention, pharmaceutical compositions are prepared by homogeneously mixing an effective amount of Compound (I) or its pharmaceutically acceptable salt with pharmaceutically acceptable carrier. It is desirable that the pharmaceutical compositions are an appropriative dosable unit for oral administration or injection administration.

In the preparation of orally administrated forms, any of useful pharmaceutically acceptable carriers are used. In the case of orally administrated liquid preparates such as suspensions and syrups, for example, water, saccharides such as sucrose, sorbitol, fructose, etc., glycols such as polyethyleneglycol, propyleneglycol, etc., oils such as sesame oil, olive oil, soybean oil, etc., antiseptics such as p-hydroxybenzoic acid esters, etc., and flavors such as strawberry flavor, peppermint etc. are used. In the case of powder, pills, capsules and tablets; vehicles such as lactose, glucose, sucrose, mannitol, etc.; disintegrators such as starch, sodium alginate, etc.; lubricants such as magnesium stearate, talc, etc.; binders such as polyvinyl alcohol, hydroxypropyl cellulose, gelatin, etc., surfactants such as fatty acid esters etc., and plasticizers such as glycerine, etc., are used. Tablets and capsules are most useful dosage form for oral administration because of easy administration. In the preparation of tablets and capsules, solid medicament carriers are used.

Injection solutions are prepared with such a carrier as distilled water, a salt solution, a glucose solution, or a mixture of a salt solution and a glucose solution.

Effective dose and the number of administration of Compound (I) or its pharmaceutically acceptable salt depend on modes of administration and ages, body weight, and symptoms, etc. of patients. It is preferable to usually administer 1 to 50 mg/kg of Compound (I) or its pharmaceutically acceptable salt daily in 2 to 3 portions.

Furthermore, Compound (I) is administrated by inhalation in the form of aerosol, finely pulverized powders, or spray solution. In the case of aerosol administration, the present compound are dissolved in a pharmaceutically acceptable solvent, for example, ethyl alcohol or a combination of miscible solvents and then mixed with a pharmaceutically acceptable propellant. The aerosol composition is used by filling it in a pressure-withstanding container composition. It is preferable that the aerosol valve is a metering valve for discharging an effective dosage of aerosol composition as determined in advance.

The present invention will be described in detail below, referring to Examples and Reference Examples. Hereafter the present invention is described by referring to the examples and the reference examples.

Example 1

6,9-Dihydro-9-methyl-3-phenyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 1):

After 3.00 g (12.6 mmol) of Compound a prepared in Reference Example 1 was suspended in 75 ml of toluene, 1.72 g (12.6 mmol) of benzoylhydrazine was added to the suspension. The mixture was refluxed for 65 hours under heating. After cooling, 200 ml of chloroform and 100 ml of a 50% saturated aqueous sodium bicarbonate aqueous solution were added, and extracted twice with 50 ml of chloroform. The extracts were combined, then the mixture was washed with a saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated. The residue was recrystallized from ethanol to afford 2.48 g (yield, 60%) of 6-(N'-benzoylhydrazino)-3,7-dihydro-7-methyl-3-n-propyl-2H-purin-2-one (Compound ma) as white needles.
Melting point: 228.9-231.1 °C

Elemental analysis: as $C_{16}H_{18}N_6O_2$			
Found (%):	C 59.05	H 5.68	N 25.84
Calcd. (%):	C 58.88	H 5.56	N 25.75

IR (KBr) νmax (cm^{-1}) : 1691, 1655, 1627, 1575
^{1}H-NMR (DMSO-d_6) δ (ppm): 10.63(s, 1H), 10.41(s, 1H), 7.92-7.84(m, 2H), 7.81(s, 1H), 7.55-7.46(m, 3H), 3.93(s, 3H), 3.81(t, 2H), 1.75-1.55(m, 2H), 0.88(t, 3H)

After 160 ml of toluene and 308 mg (1.62 mmol) of p-toluenesulfonic acid were added to 2.64 g (8.10 mmol) of the Compound ma , the mixture was refluxed for 2 hours under heating. Then 150 ml of a saturated aqueous sodium bicarbonate solution was added to the mixture. After insoluble matters were filtered off, the filtrate was extracted twice with 50 ml of chloroform and the combined extracts were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. Recrystallization from ethanol-water gave 1.68 g (yield, 67%) of Compound 1 as white needles.
Melting point: 144.6-146.1 °C (ethanol-water)

Elemental analysis: as $C_{16}H_{16}N_6O\ 0.2H_2O$			
Found (%):	C 61.37	H 5.11	N 27.01
Calcd. (%):	C 61.37	H 5.11	N 26.94

IR (KBr) νmax (cm^{-1}) : 3430(br), 1725, 1650, 1450
^{1}H-NMR ($CDCl_3$) δ (ppm): 7.75-7.65(m, 2H), 7.61(s, 1H), 7.55-7.40(m, 3H), 4.20(s, 3H), 4.25-4.15(m, 2H), 1.95-1.75(m, 2H), 0.99(t, 3H)
^{13}C-NMR ($CDCl_3$) δ (ppm): 151.3, 144.7, 143.3, 143.1, 139.6, 130.6, 130.1, 127.7, 127.2, 104.1, 45.5, 34.2, 21.3, 11.1

Example 2

6,9-Dihydro-9-methyl-6-n-propyl-3-(2-thienyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 2):

After 4.00 g (16.8 mmol) of Compound a prepared in Reference Example 1 was suspended in 15 ml of dimethylsulfoxide, 2.87 g (20.2 mmol) of thiophene-2-carboxylic hydrazide was added to the suspension. The mixture was stirred at 160 °C for 30 minutes. After cooling, 400 ml of water and 150 ml of chloroform

were added to the reaction mixture. The precipitates were collected by filtration to give 4.53 g of a light yellow powder. The NMR studies identified the powder as a mixture (approximately 9 : 1) of 3,7-dihydro-7-methyl-3-n-propyl-6-[N'-(2-thienoyl)-hydrazino]-2H-purin-2-one (Compound mb) and Compound 2. To 2.30 g of the mixture were added 20 ml of toluene, 20 ml of 1,1,2,2-tetrachloroethane and 659 mg (3.46 mmol) of p-toluenesulfonic acid monohydrate, then the solution was refluxed for 4 hours under heating. After cooling, the solution was concentrated, then 50 ml of chloroform and 50 ml of a saturated aqueous sodium bicarbonate were added. The aqueous layer was extracted twice with 50 ml of chloroform, and the extracts were combined and washed with saturated aqueous sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile gave 1.57 g (yield, 58%) of Compound 2 as a light yellow powder.
Melting point: 206.2-207.1 °C (acetonitrile)

Elemental analysis: as $C_{14}H_{14}N_6OS$			
Found (%):	C 52.94	H 4.56	N 26.40
Calcd. (%):	C 52.88	H 4.56	N 26.43

IR (KBr) νmax (cm^{-1}) : 1718, 1658
^{1}H-NMR (DMSO-d_6) δ (ppm): 8.07(s, 1H), 7.92(dd, 1H, J=3.7, 2.0Hz), 7.76(dd, 1H, J=5.1, 2.0Hz), 7.20(dd, 1H, J=5.1, 3.7Hz), 4.08(t, 2H), 4.06(s, 3H), 1.90-1.70(m, 2H), 0.92(t, 3H)

The substantially same operations as in Example 2 were performed in Examples 3 to 22 except that acylhydrazide shown in Table 8 was used in an equimolar amount instead of thiophene-2-carboxylic hydrazide.

The physicochemical data of Compounds 3 to 22 were given in Table 9.

Example 3

6,9-Dihydro-9-methyl-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 3)

Example 4

6,9-Dihydro-9-methyl-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 4)

Example 5

6,9-Dihydro-3-(2-furyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 5)

Example 6

6,9-Dihydro-9-methyl-3-(2-methyl-3-furyl)-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 6)

Example 7

6,9-Dihydro-3-(2-methoxyphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 7)

Example 8

6,9-Dihydro-3-(3-methoxyphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 8)

Example 9

6,9-Dihydro-3-(4-methoxyphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 9)

Example 10

3-(2-Chlorophenyl)-6,9-Dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 10)

Example 11

3-(3-Chlorophenyl)-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 11)

Example 12

3-(4-Chlorophenyl)-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 12)

Example 13

3-(2-Aminophenyl)-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 13)

Example 14

6,9-Dihydro-9-methyl-3-(4-methylphenyl)-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 14)

Example 15

6,9-Dihydro-9-methyl-6-n-propyl-3-(4-trifluoromethylphenyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 15)

Example 16

6,9-Dihydro-9-methyl-3-(4-nitrophenyl)-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 16)

Example 17

6,9-Dihydro-3-(4-fluorophenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 17)

Example 18

6,9-Dihydro-3-(4-dimethylaminophenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 18)

Example 19

3-(2,5-Dichlorophenyl)-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 19)

Example 20

3-(3,4-Dichlorophenyl)-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 20)

Example 21

6,9-Dihydro-3-(3,4-dimethoxyphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 21)

Example 22

6,9-Dihydro-3-(4-methoxycarbonylphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 22)

Table 8

Example No.	Acyl hydrazide	Yield (%)
3	Isonicotinic hydrazide	43
4	Nicotinic hydrazide	15
5	2-Furoic hydrazide	59
6	3-Methyl-2-furoic hydrazide	69
7	2-Methoxybenzoic hydrazide	60
8	3-Methoxybenzoic hydrazide	43
9	4-Methoxybenzoic hydrazide	63
10	2-Chlorobenzoic hydrazide	58
11	3-Chlorobenzoic hydrazide	33
12	4-Chlorobenzoic hydrazide	49
13	2-Aminobenzoic hydrazide	60
14	4-Methylbenzoic hydrazide	39
15	4-Trifluoromethylbenzoic hydrazide	80
16	4-Nitrobenzoic hydrazide	39
17	4-Fluorobenzoic hydrazide	62
18	4-(N,N-Dimethylamino)benzoic hydrazide	64
19	2,5-Dichlorobenzoic hydrazide	96
20	3,4-Dichlorobenzoic hydrazide	75
21	3,4-Dimethoxybenzoic hydrazide	69
22	4-Carbomethoxybenzoic hydrazide	76

Table 9

Compound No.	Properties	Melting point (°C) (Recrystallization solvent)	Elemental analysis (%) (upper: found lower: calcd.)	I R (KBr) cm^{-1}	M S (m/e) Relative intensity	^{1}H-NMR (Measuring solvent) δ (ppm)
3	light yellow powder	236.8 - 238.4 (Ethanol·Acetonitril)	$C_{15}H_{15}N_7O \cdot 0.8C_2H_3N$ C H N 58.20 4.91 32.15 58.27 5.13 31.93	1718, 1650	-	(DMSO-d_6) 8.72(d,2H,J=4.8Hz), 8.12(s,1H), 7.72(d,2H,J=4.8Hz), 4.10(s,3H), 4.07(t,2H), 1.90-1.70(m,2H), 0.90(t,3H)
4	white needles	170.2 - 171.8 (Acetonitril-Ether)	$C_{15}H_{15}N_7O \cdot 0.8C_2H_3N$ C H N 58.29 4.88 32.18 58.27 5.13 31.93	1715, 1650	-	(DMSO-d_6) 8.87(brs,1H), 8.70(brs,1H), 8.14(s,1H), 8.11(s,1H), 7.55(dd,1H), 4.10(s,3H), 4.06(t,2H), 1.85-1.65(m,2H), 0.90(t,3H)
5	white needles	243.5 - 248.5 (Ethanol)	$C_{14}H_{14}N_6O_2$ C H N 56.51 4.93 27.95 56.37 4.73 28.17	1712, 1651	-	($CDCl_3$) 7.67(dd,1H), 7.61(s,1H), 7.39(dd,1H), 6.59(dd,1H), 4.22(t,2H), 4.19(s,3H), 2.00-1.80(m,2H), 1.02(t,3H)
6	white needles	178.7 - 179.1 (Isopropanol)	$C_{15}H_{16}N_6O_2$ C H N 57.36 5.03 26.93 57.68 5.16 26.91	1709, 1656	-	($CDCl_3$) 7.60(s,1H), 7.39(d,1H,J=2.0Hz), 6.71(d,1H,J=2.0Hz), 4.20(t,2H), 4.19(s,3H), 2.52(s,3H), 1.93-1.75(m,2H), 1.00(t,3H)

Compound No.	Properties	Melting point (°C) (Recrystallization solvent)	Elemental analysis (%) (upper: found lower: calcd.)	I R (KBr) cm^{-1}	M S (m/e) Relative intensity	^{1}H-NMR (Measuring solvent) δ (ppm)
7	light yellow powder	164.4 - 165.1 (Isopropanol)	$C_{17}H_{18}N_6O_2$ C H N 60.18 5.21 24.82 60.34 5.36 24.84	1716, 1650, 1473, 1450	-	($CDCl_3$) 7.59(s,1H), 7.53-7.47(m,2H), 7.10-6.97(m, 2H), 4.19(s,3H), 4.15(t, 3H), 3.76(s,3H), 1.93-1.77(m,2H), 0.99(t,3H)
8	white needles	165.4 - 166.8 (Toluene)	$C_{17}H_{18}N_6O_2$ C H N 60.18 5.40 24.54 60.34 5.36 24.84	1722, 1649, 1570, 1449	-	($CDCl_3$) 7.61(s,1H), 7.43--7.26(m,3H), 7.08-7.03 (m,1H), 4.20(s,3H), 4.22-4.16(m,2H), 3.86(s,3H), 1.95-1.75(m,2H), 0.98(t, 3H)
9	white needles	161.0 - 163.3 (Toluene-Cyclohexane)	$C_{17}H_{18}N_6O_2$ C H N 60.55 5.49 25.24 60.34 5.36 24.84	3105, 2960, 1715, 1650, 1483	-	(DMSO-d_6) 8.07(s,1H), 7.64(d,2H,J=6.8Hz), 7.03 (d,2H,J=6.8Hz), 4.08(s, 3H), 4.04(t,2H), 3.84(s, 3H), 1.80-1.60(m,2H), 0.89(t,3H)
10	white needles	163.4 - 165.2 (Toluene-Cyclohexane)	$C_{16}H_{15}N_6OCl$ C H N 56.19 4.28 24.42 56.06 4.41 24.52	1721, 1649, 1567, 1449, 1436	-	(DMSO-d_6) 8.12(s,1H), 7.65-7.45(m,4H), 4.10(s, 3H), 4.03(t,2H), 1.80-1.60(s,2H), 0.87(t,3H)

Compound No.	Properties	Melting point (°C) (Recrystallization solvent)	Elemental analysis (%) (upper: found lower: calcd.)	I R (KBr) cm^{-1}	M S (m/e) Relative intensity	^{1}H-NMR (Measuring solvent) δ (ppm)
11	white needles	142.9 - 143.8 (Ethanol)	$C_{16}H_{16}N_6OCl$ C H N 56.40 4.23 24.63 56.06 4.41 24.52	1708, 1659, 1447, 1299	-	($CDCl_3$) 7.78-7.77(m,1H), 7.66-7.62(m,1H), 7.62(s, 1H), 7.51-7.39(m,2H), 4.21(s,3H), 4.20(t,2H), 1.95-1.75(m,2H), 0.99 (t,3H)
12	white needles	175.1 - 177.0 (Toluene-Cyclohexane)	$C_{16}H_{15}N_6OCl$ C H N 55.79 4.45 24.70 56.06 4.41 24.52	1728, 1657, 1470, 1450	-	(DMSO-d_6) 8.09(s,1H), 7.73(d,2H,J=7.5Hz), 7.56 (d,2H,J=7.5Hz), 4.09(s, 3H), 4.05(t,2H), 1.85-1.65(m,2H), 0.89(t,3H)
13	light yellow powder	177.1 - 177.8 (Ethanol-water)	$C_{16}H_{17}N_7O$ C H N 59.10 5.47 30.67 59.43 5.30 30.32	3420, 3350, 1710, 1655, 1448	-	(DMSO-d_6) 8.06(s,1H), 7.20-7.05(m,2H), 6.70 (d,1H), 6.57(t,1H), 5.20(brs,2H), 4.09(s, 3H), 4.00(t,2H), 1.80-1.60(m,2H), 0.88(t,3H)
14	white needles	169.9 - 171.2	$C_{17}H_{18}N_6O$ C H N 63.62 5.53 26.39 63.34 5.63 26.07	1708, 1646, 1478, 1445	-	($CDCl_3$) 7.64(d,2H,J= 8.0Hz), 7.60(s,1H), 7.29(d,2H,J=8.0Hz), 4.20(s,3H), 4.19(t,2H), 2.43(s,3H), 1.93-1.77 (m,2H), 0.98(t,3H)

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Compound No.	Properties	Melting point (°C) (Recrystallization solvent)	Elemental analysis (%) (upper: found lower: calcd.)	I R (KBr) cm^{-1}	M S (m/e) Relative intensity	^{1}H-NMR (Measuring solvent) δ (ppm)
15	white needles	205.8 - 207.0 (Isopropanol)	$C_{17}H_{15}N_6F_3O$ C H N 54.0 3.78 22.13 54.25 4.02 22.33	1707, 1652, 1574, 1450, 1409	-	($CDCl_3$) 7.91(d,2H,J=8.0 Hz), 7.75(d,2H,J=8.0Hz), 7.64(s,1H), 4.22(s,3H), 4.20(t,2H), 1.97-1.77(m, 2H), 1.00(t,3H)
16	white needles	117.0 - 117.2 (Toluene)	$C_{16}H_{15}N_7O_3 \cdot 0.3H_2O$ C H N 53.56 4.27 27.46 53.57 4.38 27.33	1707, 1655, 1515, 1449	-	($CDCl_3$) 8.35(d,2H,J=9.0 Hz), 7.98(d,2H,J=9.0Hz), 7.66(s,1H), 4.22(s,3H), 4.21(t,2H), 1.95-1.77 (m,2H), 1.00(t,3H)
17	light yellow needles	192.0 - 193.9 (Ethanol-water)	——	3400, 1722, 1657, 1482, 1451	326(M^+, 100) 297(12) 284(33) 283(42) 163(12)	($CDCl_3$) 7.77(dd,1H,J= 6.3,8.7Hz), 7.61(s,1H), 7.18(dd,1H,J=8.7,8.7Hz), 4.22(t,2H), 4.20(s,3H), 1.93-1.75(m,2H), 0.99 (t,3H)
18	white needles	255.9 - 256.2 (Isopropanol)	$C_{18}H_{21}N_7O \cdot 1/5HCl$ C H N 60.36 5.89 27.36 60.27 5.96 27.33	1706, 1651, 1612, 1478, 1449	-	($CDCl_3$) 7.73(d,2H,J=9.0 Hz), 7.59-7.04(brd,2H), 4.20(s,3H), 4.19(t,2H), 3.08(s,6H), 2.00-1.75 (m,2H), 0.99(t,3H)

Compound No.	Properties	Melting point (°C) (Recrystallization solvent)	Elemental analysis (%) (upper: found lower: calcd.)	I R (KBr) cm^{-1}	M S (m/e) Relative intensity	^1H-NMR (Measuring solvent) δ (ppm)
19	white needles	257.3 - 258.1 (Acetonitril)	$C_{16}H_{14}N_6Cl_2O$ C H N 50.98 3.54 22.15 50.94 3.74 22.28	1722, 1650, 1571, 1448	-	($CDCl_3$) 7.63(s,1H), 7.56(m,1H), 7.45-7.43 (m,2H), 4.21(s,3H), 4.17(t,3H), 1.93-1.75 (m,2H), 0.97(t,3H)
20	white needles	175.0 - 176.1 (Ethanol-water)	$C_{16}H_{14}N_6OCl_2 \cdot 0.6H_2O$ C H N 49.27 3.69 21.39 49.52 3.95 21.66	1720, 1650, 1571, 1450	378(M^++2, 66), 376 (M^+, 100) 336(22), 335(32), 334(35), 333(37)	($CDCl_3$) 7.90-7.89(m,1H), 7.63(s,1H), 7.64-7.54(m, 2H), 4.20(s,3H), 4.19 (t,2H), 1.97-1.78(m,2H), 1.00(t,3H)
21	white powder	211 - 215 (Dioxane)	$C_{18}H_{20}N_6O_3$ C H N 58.46 5.30 23.16 58.67 5.48 22.82	1723, 1652, 1499, 1447	-	($CDCl_3$) 7.60(s,1H), 7.38-7.33(m,2H), 6.98 (d,1H,J=8.2Hz), 4.21(t, 2H), 4.20(s,3H), 3.95 (s,3H), 3.94(s,3H), 1.97-1.78(m,2H), 0.99 (t,3H)
22	white needles	251.3 - 252.9 (Toluene)	$C_{18}H_{18}N_6O_3$ C H N 59.13 5.17 22.82 59.01 4.95 22.94	1715, 1653, 1611, 1568, 1439	-	(DMSO-d_6) 8.11(s,1H), 8.06(d,2H,J=8.5Hz), 7.86(d,2H,J=8.6Hz), 4.10(s,3H), 4.05(t,2H), 3.91(s,3H), 1.82-1.62 (m,2H), 0.89(t,3H)

Example 23

6,9-Dihydro-3-(4-carboxyphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 23):

After 3.00 g (8.20 mmol) of Compound 22 prepared in Example 22 was dissolved in 30 ml of dimethylsulfoxide, 11.7 g (82 mmol) of lithium iodide was added and the mixture was stirred at 140°C for 13 hours. After cooling, 500 ml of water was added to the solution followed by extraction 10 times with 50 ml of chloroform-methanol (10 : 1). The extracts were combined and washed with 0.2 M sodium thiosulfate aqueous solution and with a saturated aqueous sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% methanol/chloroform), and triturated with 10 ml of methanol to afford 1.40 g (yield, 49%) of Compound 23 as a light yellow powder.
Melting point: >315°C
IR (KBr) νmax (cm^{-1}) : 3400, 1728, 1700, 1650, 1593, 1553
^{1}H-NMR (DMSO-d_6) δ (ppm): 8.09(s, 1H), 8.05(d, 2H, J=8.3Hz), 7.74(d, 2H, J=8.3Hz), 4.09(s, 3H), 4.04(t, 2H), 1.82-1.62(m, 2H), 0.89(t, 3H)
MS (m/e: relative intensity): 352(M^+, 100), 310(59), 309(79)

Example 24

6,9-Dihydro-3,9-dimethyl-6-n-propyl-5H-1,2,4-triazolo-[3,4-i]purin-5-one (Compound 24):

After 100 ml of toluene and 1.49 g (20.2 mmol) of acetohydrazide were added to 4.00 g (16.8 mmol) of Compound a prepared in Reference Example 1, the mixture was refluxed for 53 hours under heating. After cooling, the solution was concentrated, 100 ml of chloroform and 50 ml of 50% saturated sodium bicarbonate aqueous solution were added and the aqueous layer was extracted twice with 30 ml of chloroform. The extracts were combined and washed with a saturated aqueous sodium chloride. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 2% methanol/chloroform) to afford 1.39 g (yield, 34%) of Compound 24 as a white powder.
Melting point: 191.9-193.6°C (acetonitrile-ethanol)

Elemental analysis: as $C_{11}H_{14}N_6O \cdot 3/4CH_3CN \cdot 1/5C_2H_5OH$			
Found (%):	C 54.21	H 5.99	N 32.84
Calcd. (%):	C 54.12	H 6.14	N 33.03

IR (KBr) νmax (cm^{-1}) : 1715, 1655, 1450
^{1}H-NMR ($CDCl_3$) δ (ppm): 7.57(s, 1H), 4.19(t, 2H), 4.14(s, 3H), 2.95(s, 3H), 1.95-1.80(m, 2H), 1.02(t, 3H)
^{13}C-NMR ($CDCl_3$) δ (ppm): 149.1, 145.7, 143.1, 142.7, 139.2, 104.2, 45.18, 34.1, 21.3, 13.4, 11.1

Example 25

6,9-Dihydro-3-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]-purin-5-one (Compound 25):

After 5 ml of dimethylsulfoxide and 730 mg (9.82 mmol) of acetohydrazide were added to 2.00 g (8.93 mmol) of Compound b prepared in Reference Example 2, the mixture was stirred at 160°C for 30 minutes. After cooling, the 200 ml of water and 50 ml of chloroform were added to the solution. After fractionation,

the aqueous layer was extracted twice with 50 ml of chloroform. The extracts were combined and washed twice with water and once with a saturated aqueous sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 5% methanol/chloroform) to afford 1.16 mg (yield, 52%) of Compound 25 as a white powder.

Melting point: 298.0-299.2° C (ethanol)

Elemental analysis: as $C_{10}H_{12}N_6 \cdot 0.1H_2O$			
Found (%):	C 51.58	H 5.25	N 35.62
Calcd. (%):	C 51.32	H 5.25	N 35.90

IR (KBr) νmax (cm^{-1}) : 1715, 1662

^{1}H-NMR (DMSO-d_6) δ (ppm): 13.78(brs, 1H), 8.01(s, 1H), 4.08(t, 2H), 2.76(s, 3H), 1.95-1.70(m, 2H), 0.92(t, 3H)

Example 26

8-Cyclopentyl-6,9-dihydro-6-n-propyl-3-phenyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 26):

After 2.00 g (6.85 mmol) of Compound c prepared in Reference Example 3 was dissolved in 50 ml of toluene, 1.40 g (10.28 mmol) of benzoylhydrazine was added to the solution. The mixture was refluxed for 4 hours and a half under heating. After cooling, 100 ml of chloroform was added to the reaction solution. The precipitates were collected by filtration to afford 2.22 g (yield, 86%) of 6-(N′-benzoylhydrazino)-8-cyclopentyl-3,7-dihydro-3-n-propyl-2H-purin-2-one (Compound mc) as a white powder.

Melting point: 223.1-224.9° C

Elemental analysis: as $C_{20}H_{24}N_6O_2$			
Found (%):	C 63.10	H 6.30	N 22.01
Calcd. (%):	C 63.14	H 6.36	N 22.09

IR (KBr) νmax (cm^{-1}) : 1680, 1614, 1574, 1504

^{1}H-NMR (DMSO-d_6) δ (ppm): 12.8-12.3(brs, 1H), 10.7-10.2(br, 2H), 8.04-7.89(m, 2H), 7.65-7.48(m, 3H), 3.83-(t, 2H), 3.30-3.10(m, 1H), 2.20-1.60(m, 10H), 0.87(t, 3H)

1.07 g of Compound 26 as white needles was obtained from 1.89 g (4.97 mmol) of the Compound mc by similar manner to Example 1 (yield, 59%).

Melting point: 252.9-254.5° C (ethanol-water)

Elemental analysis: as $C_{20}H_{22}N_6O$			
Found (%):	C 66.54	H 6.20	N 23.25
Calcd. (%):	C 66.28	H 6.12	N 23.19

IR (KBr) νmax (cm^{-1}) : 1720, 1660

^{1}H-NMR (DMSO-d_6) δ (ppm): 13.55(brs, 1H), 7.80-7.60(m, 2H), 7.55-7.40(m, 3H), 4.05(t, 2H), 3.35-3.15(m, 1H), 2.15-1.55(m, 10H), 0.89(t, 3H)

Example 27

8-Cyclopentyl-6,9-dihydro-3-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 27):

The procedure was performed in a manner similar to Example 26 except for using 760 mg (10.28 mmol) of acetohydrazide instead of benzoylhydrazine. Thus, 1.92 g (yield, 88%) of 8-cyclopentyl-6-(N'-acetylhydrazino)-3,7-dihydro-3-n-propyl-2H-purin-2-one (Compound md) was obtained as a white powder.
Melting point: >270 °C

Elemental analysis: as $C_{15}H_{22}N_6O_2$			
Found (%):	C 56.25	H 6.98	N 26.34
Calcd. (%):	C 56.59	H 6.97	N 26.40

IR (KBr) νmax (cm^{-1}) : 1667, 1651, 1539

1.51 g of Compound 27 as white needles was obtained from 1.84 g (5.79 mmol) of Compound md by a similar manner to Example 1 (yield, 87%).
Melting point: 307.6-309.4 °C (isopropanol)

Elemental analysis: as $C_{15}H_{20}N_6O_1$			
Found (%):	C 60.33	H 6.84	N 27.65
Calcd. (%):	C 59.98	H 6.71	N 27.98

IR (KBr) νmax (cm^{-1}) : 1720, 1660
^{1}H-NMR (DMSO-d_6) δ (ppm): 13.39(brs, 1H), 4.04(t, 2H), 3.30-3.10(m, 1H), 2.75(s, 3H), 2.10-1.55(m, 10H), 0.91(t, 3H)

Example 28

6-Benzyl-6,9-dihydro-9-methyl-3-phenyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 28):

Using 4.00 g (14.0 mmol) of Compound h in Reference Example 8 and 2.28 g (16.8 mmol) of benzoyl hydrazine, the procedure was carried out in a manner similar to Example 2 to give 2.69 g (yield, 54%) of Compound 28 as light yellow needles.
Melting point: 255.3-256.9 °C (toluene)

Elemental analysis: as $C_{20}H_{16}N_6O \cdot H_2O$			
Found (%):	C 67.22	H 4.37	N 23.16
Calcd. (%):	C 67.07	H 4.56	N 23.46

IR (KBr) νmax (cm^{-1}) : 1717, 1650, 1567, 1451
^{1}H-NMR (DMSO-d_6) δ (ppm): 8.09(s, 1H), 7.72-7.67(m, 2H), 7.56-7.44(m, 3H), 7.40-7.35(m, 2H), 7.34-7.20(m, 3H), 5.28(s, 2H), 4.10(s, 3H)

Example 29

6,9-Dihydro-3,6-diphenyl-9-methyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 29):

Except that 3.50 g (12.9 mmol) of Compound k in Reference Example 10 and 2.10 g (15.4 mmol) of benzoylhydrazine were used, the procedure was performed in a manner similar to Example 2. Thus, 962

mg (yield, 22%) of Compound 29 was obtained as a white powder.
Melting point: 267.9-269.7° C (N,N'-dimethylformamide-water)

Elemental analysis: as $C_{19}H_{14}N_6O$			
Found (%):	C 66.35	H 3.81	N 24.84
Calcd. (%):	C 66.66	H 4.12	N 24.55

IR (KBr) νmax (cm^{-1}) : 1717, 1655, 1429
^{1}H-NMR (DMSO-d_6) δ (ppm): 7.97(s, 1H), 7.73-7.67(m, 2H), 7.57-7.41(m, 8H), 4.11(s, 3H)

Example 30

6,9-Dihydro-3-phenyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 30):

The procedure was performed in a manner similar to Example 2 except for using 8.27 g (24.0 mmol) of Compound f obtained in Reference Example 6 and 3.93 g (28.8 mmol) of benzoylhydrazide. Thus, 6.90 g (yield, 69%) of 8-benzyloxymethyl-6,9-dihydro-3-phenyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound me) was obtained as a light yellow powder.
^{1}H-NMR (90 MHz; $CDCl_3$) δ (ppm): 7.75(s, 1H), 7.80-7.65(m, 2H), 7.60-7.45(m, 3H), 7.24(brs, 5H), 5.93(s, 2H), 4.78(s, 2H), 4.18(t, 2H), 2.00-1.60(m, 2H), 0.99(t, 3H)

After 6.71 g (16.2 mmol) of the Compound me was suspended in 325 ml of toluene, 32.4 ml of 1 M boron tribromide in methylene chloride was dropwise added to the suspension under ice cooling. The mixture was stirred at room temperature for 2 hours. The reaction mixture was poured onto ice water followed by extraction 3 times with 100 ml of chloroform. The extracts were combined and washed with a saturated aqueous sodium chloride. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The precipitates were collected by filtration and then washed with methanol. The crystals were recrystallized from isopropanol to give 2.52 g (yield, 53%) of Compound 30 as white needles.
Melting point: 272.8-280.0° C (acetonitrile)

Elemental analysis: as $C_{15}H_{14}N_6O \cdot 0.1 H_2O \cdot 0.5C_2H_3N$			
Found (%):	C 60.69	H 4.75	N 28.83
Calcd. (%):	C 60.69	H 5.00	N 28.75

IR (KBr) νmax (cm^{-1}) : 1720, 1660
^{1}H-NMR (DMSO-d_6) δ (ppm): 14.10-13.80(brs, 1H), 8.11(s, 1H), 7.80-7.70(m, 2H), 7.60-7.45(m, 3H), 4.08(t, 2H), 1.90-1.70(m, 2H), 0.90(t, 3H)

Example 31

6,9-Dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 31):

The procedure was performed in a manner similar to Example 2 except for using 4.00 g (11.6 mmol) of Compound f prepared in Reference Example 6 and 1.91 g (14.0 mmol) of isonicotinic hydrazide. Thus, 2.32 g (yield, 48%) of 8-benzyloxymethyl-6,9-dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound mf) obtained as a yellow powder.
^{1}H-NMR (90 MHz; $CDCl_3$) δ (ppm): 8.73(d, 2H, J = 8.9Hz), 7.78(s, 1H), 7.69(d, 2H, J = 8.9Hz), 7.23(brs, 5H), 5.93(s, 2H), 4.78(s, 2H), 4.20(t, 2H), 2.00-1.65(m, 2H), 1.01(t, 3H)

1.09 g of Compound 31 as white needles was obtained from 2.10 g of Compound mf by the similar

elimination reaction of the protecting group to Example 30 (yield, 73%).
Melting point: >330° C (DMF-dioxan-water)

Elemental analysis: as $C_{14}H_{13}N_7O \cdot 0.8H_2O$			
Found (%):	C 32.02	H 4.51	N 32.02
Calcd. (%):	C 31.67	H 4.75	N 31.66

IR (KBr) νmax (cm^{-1}) : 1732, 1659, 1603, 1568, 1514,
^{1}H-NMR (DMSO-d_6) δ (ppm): 14.03(s, 1H), 8.71(d, 2H, J = 5.5Hz), 8.14(s, 1H), 7.73(m, 2H), 4.10(t, 2H), 1.85-1.65(m, 2H), 0.91(t, 3H)

Example 32

6,9-Dihydro-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 32):

The procedure was performed in a manner similar to Example 2 except for using 3.50 g (10.2 mmol) of Compound f prepared in Reference Example 6 and 1.68 g (12.2 mmol) of nicotinic acid hydrazide. Thus, 2.87 g (yield, 53%) of 8-benzyloxymethyl-6,9-dihydro-6-n-propyl-3-(3-pyridyl)-5H- 1,2,4-triazolo[3,4-i]purin-5-one (Compound mg) was obtained as a yellow powder.
^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm): 9.05-8.90(m, 1H), 8.80-8.65(m, 1H), 8.20-7.95(m, 1H), 7.77(s, 1H), 7.55-7.25(m, 1H), 7.23(brs, 5H), 5.93(s, 2H), 4.78(s, 2H), 4.20(t, 2H), 2.05-1.70(m, 2H), 1.01(t, 3H)

503 mg of Compound 32 as white needles was obtained (yield, 28%) from 2.50 g (6.02 mmol) of Compound mg and 4 equivalents of boron tribromide by the similar elimination reaction of the protecting group to Example 30.
Melting point: 277.2-278.2° C (dioxan)
IR (KBr) νmax (cm^{-1}) : 1721, 1654, 1571
^{1}H-NMR (DMSO-d_6) δ (ppm): 14.15-13.80(br, 1H), 8.90(brs, 1H), 8.71(brs, 1H), 8.18-8.14(m, 1H), 8.12(s, 1H), 7.56(dd, 1H, J = 5.0, 7.5Hz), 4.10(t, 2H), 1.85-1.65(m, 2H), 0.91(t, 3H)
MS (m/e; relative intensity): 285(M^+, 100), 253(68)

Elemental analysis: as $C_{14}H_{13}N_7O \cdot 0.2H_2O$			
Found (%):	C 56.12	H 4.39	N 32.82
Calcd (%):	C 56.26	H 4.52	N 32.80

Example 33

6,9-Dihydro-6-n-propyl-3-(2-thienyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 33):

The procedure was performed in a manner similar to Example 2 except for using 4.50 g (13.1 mmol) of Compound f obtained in Reference Example 6 and 2.23 g (15.7 mmol) of 2-thiophenecarboxylic acid hydrazide . Thus 2.87 g (yield, 52%) of 8-benzyloxymethyl-6,9-dihydro-6-n-propyl-3-(2-thienyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound mh) was obtained as a light red powder.
^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm): 8.05-7.90(m, 1H), 7.74(s, 1H), 7.60-7.45(m, 1H), 7.35-7.05(m, 6H), 5.92(s, 2H), 4.77(s, 2H), 4.21(t, 2H), 2.05-1.65(m, 2H), 1.03(t, 3H)

1.63 g of Compound 33 as white needles was obtained from 2.65 g (6.31 mmol) of Compound mh by the similar elimination reaction of the protecting group to Example 30 (yield, 87%).
Melting point: 286.8-290.9° C (N,N-dimethylformamide-water)

Elemental analysis: as $C_{13}H_{12}N_6OS$			
Found (%):	C 52.18	H 3.74	N 28.02
Calcd. (%):	C 51.99	H 4.03	N 27.98

IR (KBr) νmax (cm^{-1}) : 1721, 1660
^{1}H-NMR (DMSO-d_6) δ (ppm): 13.93(brs, 1H), 8.08(s, 1H), 7.93(dd, 1H, J=1.2, 3.6Hz), 7.76(dd, 1H, J=1.2, 5.2Hz), 7.19(dd, 1H, J=3.6, 5.2Hz), 4.13(t, 2H), 1.90-1.70(m, 2H), 0.93(t, 3H)

Example 34

6-Benzyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 34):

The procedure was carried out in a manner similar to Example 31 except for using 3.50 g (8.90 mmol) of Compound m obtained in Reference Example 11 instead of Compound f . Thus, 1.06 g (yield, 36%) of Compound 34 (free form) was obtained as a light yellow powder. The powder was suspended in 10 ml of methanol and 1 ml of hydrogen chloride-saturated methanol solution was added to the suspension. The precipitates were collected by filtration to afford 560 mg (yield, 45%) of the hydrochloride of Compound 34 as a yellow powder.
Melting point: >290 °C
IR (KBr) νmax (cm^{-1}) : 1712, 1655, 1631
^{1}H-NMR (90MHz; DMSO-d_6) δ (ppm): 9.10-8.75(br, 2H), 8.20-8.05(m, 2H), 8.14(s, 1H), 7.50-7.10(m, 5H), 5.23(s, 2H)
MS (m/e; relative intensity): 343(M^+, 76), 91(100)

Example 35

6,9-Dihydro-6,9-di-n-propyl-3-phenyl-5H-1,2,4-triazolo-[3,4-i]purin-5-one (Compound 35):

After 500 mg (1.70 mmol) of Compound 30 obtained in Example 30 was dissolved in 5 ml of N,N'-dimethylformamide, 81.6 mg (2.04 mmol) of 60% sodium hydride was added to the solution at 0 °C. 15 minutes after, 0.25 ml (2.51 mmol) of propyl iodide was added to the reaction solution at 0 °C. The solution was stirred at room temperature for 30 minutes. After 20 ml of saturated ammonium chloride was added to the reaction solution at 0 °C, the mixture was extracted 3 times with 30 ml of chloroform. The extracts were combined and washed with a saturated sodium chloride aqueous solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent: 2% methanol/chloroform) to afford 434 mg (yield, 76%) of Compound 35 as white needles.
Melting point: 215.1-216.8 °C (ethanol)

Elemental analysis: as $C_{18}H_{20}N_6O$			
Found (%):	C 64.10	H 6.08	N 25.08
Calcd. (%):	C 64.27	H 5.99	N 24.98

IR (KBr) νmax (cm^{-1}) : 1710, 1651
^{1}H-NMR (DMSO-d_6) δ (ppm): 8.15(s, 1H), 7.73-7.66(m, 2H), 7.53-7.40(m, 3H), 4.39(t, 2H), 4.06(t, 2H), 2.10-1.95(m, 2H), 1.83-1.66(m, 2H), 0.91(t, 3H), 0.90(t, 3H)

Example 36

6,9-Dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 36):

After 15 ml of ethyl orthoformate was added to 800 mg (3.60 mmol) of Compound n prepared in Reference Example 12, the mixture was refluxed for 2 hours under heating. After the reaction solution was allowed to stand over day and night, the precipitates were collected by filtration to give 760 mg (yield, 91%) of Compound 36 as a light red plate.
Melting point: 217.8-218.2 °C
IR (KBr) νmax (cm^{-1}) : 1696, 1649
^{1}H-NMR (DMSO-d_6) δ (ppm): 9.16(s, 1H), 8.02(s, 1H), 4.10(t, 2H), 4.04(s, 3H), 2.00-1.55(m, 2H), 0.92(t, 3H)
MS (m/e: relative intensity): 232(M^+, 48), 190(84), 189(100)

Example 37

6-Benzyl-6,9-dihydro-3-methyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 37):

The procedure was performed in a manner similar to Example 25 except for using 2.20 g (8.08 mmol) of Compound l prepared in Reference Example 8. Thus, 1.40 g (yield, 62%) of Compound 37 was obtained as a light yellow powder.
Melting point: 308.9-310.3 °C

Elemental analysis: as $C_{14}H_{12}N_6O \cdot 0.2H_2O$			
Found (%):	C 59.17	H 3.99	N 30.01
Calcd. (%):	C 59.23	H 4.40	N 29.60

IR (KBr) νmax (cm^{-1}) : 1720, 1659
^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.83(brs, 1H), 8.03(s, 1H), 7.45-7.20(m, 5H), 5.30(s, 2H), 2.76(s, 3H)

Example 38

6-n-Butyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 38):

The procedure was performed in a manner similar to Example 2 except for using 5.61 g (15.7 mmol) of Compound r prepared in Reference Example 16 and 2.36 g (17.2 mmol) of isonicotinic hydrazide. Thus, 4.42 g of (yield, 66%) of 8-benzyloxymethyl-6-n-butyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound mi) was obtained as a yellow powder.
^{1}H-NMR (90MHz; $\overline{CD}Cl_3$) δ (ppm): 8.71(d, 2H, J=8.8Hz), 7.78(s, 1H), 7.68(d, 2H, J=8.8Hz), 7.22(brs, 5H), 5.93(s, 2H), 4.77(s, 2H), 4.22(t, 2H), 2.00-1.25(m, 4H), 0.98(t, 3H).
2.82 g of Compound 38 as white needles was obtained (yield, 89%) from 4.42 g of Compound mi by the similar elimination reaction of the protecting group to in Example 30.
Melting point: 271.0-272.3 °C (isopropanol)

Elemental analysis: as $C_{15}H_{15}N_7O$			
Found (%):	C 58.13	H 4.97	N 31.49
Calcd. (%):	C 58.24	H 4.89	N 31.70

IR (KBr) νmax (cm^{-1}) : 1718, 1654
^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.95(brs, 1H), 8.70(d, 2H, J=5.6Hz), 8.12(s, 1H), 7.72(d, 2H, J=5.6Hz), 4.11(t, 2H), 1.80-1.65(m, 2H), 1.45-1.30(m, 2H), 0.89(t, 3H)

Example 39

9-Benzyl-6,9-dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 39):

Except that 7.00 g (17.9 mmol) of Compound s obtained in Reference Example 17 and 2.71 g (19.7 mmol) of isonicotinic hydrazide were used, the procedure was performed in a manner similar to Example 2. Thus, 4.29 g of (yield, 62%) of Compound 39 was obtained as light yellow needles.
Melting point: 210.2-211.8° C (acetonitrile)

Elemental analysis: as $C_{21}H_{19}N_7O \cdot 0.1H_2O$			
Found (%):	C 65.31	H 4.87	N 24.92
Calcd. (%):	C 65.14	H 5.00	N 25.32

IR (KBr) νmax (cm^{-1}) : 1728, 1714, 1641
^{1}H-NMR (DMSO-d_6) δ (ppm) : 8.70(d, 1H, J=5.8Hz), 8.36(s, 1H), 7.72(d, 1H, J=5.8Hz), 7.55-7.50(m, 2H), 7.40-7.25(m, 3H), 5.68(s, 2H), 4.06(t, 2H), 1.85-1.65(m, 2H), 0.90(t, 3H)

Example 40

6,9-Dihydro-6,9-di-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 40):

Except that 2.50 g (8.50 mmol) of Compound t in Reference Example 18 and 1.40 g (10.2 mmol) of isonicotinic hydrazide were used, the procedure was performed in a manner similar to Example 2. Thus, 2.38 g of (yield, 83%) of Compound 40(free form) was obtained as light yellow needles.
Melting point: 198.0-200.1° C (isopropanol)

Elemental analysis: as $C_{17}H_{19}N_7O$			
Found (%):	C 60.29	H 5.80	N 29.30
Calcd. (%):	C 60.52	H 5.68	N 29.06

IR (KBr) νmax (cm^{-1}) : 1715, 1647
NMR ($CDCl_3$) δ (ppm) : 8.76(d, 2H, J=5.2Hz), 7.72(d, 2H, J=5.2Hz), 7.66(s, 1H), 4.46(t, 2H) 4.24(t, 2H), 2.20-2.08(m, 2H), 1.98-1.80(m, 2H), 1.05-0.98(m, 6H)

After 2.00 g (5.93 mmol) of free form of Compound 40 was suspended in 20 ml of methanol, 5 ml of hydrochloride-saturated ethanol was added to the suspension. The suspension was stirred for 10 minutes, and the solvent was evaporated under reduced pressure. Recrystallization from ethanol gave 1.48 g of Compound 40 (yield, 67%) as yellow needles.
Melting point: 193.8-199.0° C

Elemental analysis: as $C_{17}H_{19}N_7O \cdot HCl$			
Found (%):	C 54.71	H 5.64	N 26.50
Calcd. (%):	C 54.62	H 5.39	N 26.23

IR (KBr) νmax (cm^{-1}) : 1710, 1652, 1632, 1592
^{1}H-NMR ($CDCl_3$) δ (ppm) : 8.86(d, 2H, J=6.9Hz), 8.50(d, 2H, J=6.9Hz), 7.76(s, 1H), 4.49(d, 2H), 4.29(d, 2H), 2.20-1.80(m, 4H), 1.05-0.95(m, 6H)

Example 41

9-Methyl-6-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound 41):

After 24 ml of dimethylsulfoxide and 1.23 g (11.8 mmol) of ethyl carbazate were added to 2.35 g (9.87 mmol) of Compound a prepared in Reference Example 1, the mixture was stirred at 160 °C for 2 hours. After cooling, 200 ml of water was added to the mixture. The precipitates were collected by filtration and recrystallized from ethanol to afford 1.10 g (yield, 45%) of Compound 41 as a white powder.
Melting point: 299.3-301.1 °C (ethanol)

Elemental analysis: as $C_{10}H_{12}N_6O_2$			
Found (%):	C 48.21	H 4.73	N 33.92
Calcd. (%):	C 48.38	H 4.87	N 33.85

IR (KBr) νmax (cm^{-1}) : 1757, 1653
^{1}H-NMR (DMSO-d_6) δ (ppm) : 11.99(s, 1H), 7.91(s, 1H), 3.90(t, 2H), 3.86(s, 3H), 1.80-1.60(m, 2H), 0.87(t, 3H)

Example 42

6-Benzyl-9-methyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo-[3,4-i]purin-3,5-dione (Compound 42):

The procedure was performed in a manner similar to Example 41 except for using 2.0 g (7.0 mmol) of Compound h prepared in Reference Example 8 and 870 mg (8.4 mnol) of ethyl carbazate. Thus, 1.83 g (yield, 80%) of Compound 42 was obtained as light yellow needles.
Melting point: 295 °C (dioxane-water)

Elemental analysis: as $C_{14}H_{12}N_6O_2$			
Found (%):	C 56.51	H 3.79	N 28.47
Calcd. (%):	C 56.74	H 4.09	N 28.37

IR (KBr) νmax (cm^{-1}) : 1772, 1760, 1694, 1640
^{1}H-NMR (DMSO-d_6) δ (ppm) : 11.99(brs, 1H), 7.90(s, 1H), 7.42-7.25(m, 5H), 5.13(s, 2H), 3.87(s, 3H)

Example 43

8-Cyclopentyl-6-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound 43):

The procedure was performed in a manner similar to Example 41 except for using 1.50 g (5.14 mmol) of Compound e obtained in Reference Example 5 and 640 mg (6.17 mmol) of ethyl carbazate. Thus, 571 mg (yield, 37%) of Compound 43 was obtained as white needles.
Melting point: 297.1-298.8 °C (dioxane-water)

Elemental analysis: as $C_{14}H_{18}N_6O_2 \cdot 0.1C_4H_8O_2$			
Found (%):	C 55.27	H 6.08	N 26.82
Calcd. (%):	C 55.59	H 6.09	N 27.01

IR (KBr) νmax (cm^{-1}) : 1751, 1694, 1654
^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.09(brs, 1H), 11.81(s, 1H), 3.91(t, 2H), 3.27-3.13(m, 1H), 2.10-1.60(m, 10H), 0.89(t, 3H)

Example 44

6,9-Di-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound 44):

The procedure was performed in a manner similar to Example 41 except for using 1.88 g (7.07 mmol) of Compound o prepared in Reference Example 13 and 0.880 g (8.48 mmol) of ethyl carbazate. Thus, 1.65 g (yield, 85%) of Compound 44 was obtained as white needles.
Melting point: 216.7-218.0 °C (isopropanol)

Elemental analysis: as $C_{12}H_{16}N_6O_2 \cdot 0.1C_3H_8O$			
Found (%):	C 52.34	H 5.84	N 29.91
Calcd. (%):	C 52.33	H 6.00	N 29.77

IR (KBr) νmax (cm^{-1}) : 1768, 1647
^{1}H-NMR ($CDCl_3$) δ (ppm) : 10.85(brs, 1H), 7.51(s, 1H), 4.17(t, 2H), 4.10(t, 2H), 2.05-1.80(m, 4H), 1.00(t, 3H), 0.98(t, 3H)

Example 45

6-n-Propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound 45):

The procedure was performed in a manner similar to Example 41 except for using 3.98 g (11.6 mmol) of Compound f obtained in Reference Example 6 and 1.45 g (13.9 mmol) of ethyl carbazate. Thus, 1.05 g (yield, 19%) of 2,9-dibenzyloxymethyl-6-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound mj) was obtained as a light yellow powder.
Melting point: 88.9-90.3 °C
IR (KBr) νmax (cm^{-1}) : 1764, 1700, 1653
^{1}H-NMR ($CDCl_3$) δ (ppm) : 7.57(s, 1H), 7.40-7.10(m, 10H), 5.66(s, 2H), 5.33(s, 2H), 4.69(s-like, 4H), 4.05(t, 2H), 2.00-1.60(m, 2H), 1.00(t, 3H)
MS (m/e: relative intensity): 474(M^+, 28), 414(35), 225(7), 91(100)
After 739 mg (1.56 mmol) of Compound mj was suspended in 40 ml of toluene, 4.18 ml (4.18 mmol) of a solution of 1 M boron tribromide/methylene chloride was dropwise added to the suspension at -78 °C. The mixture was stirred at 0 °C for an hour. The mixture was poured onto ice water. 2 N sodium hydroxide aqueous solution was added to adjust to pH 7.5. The mixture was washed 3 times with chloroform. After the aqueous layer was concentrated under reduced pressure, the residue was purified by 200 ml of DIAION HP-40 (manufactured by Mitsubishi Chemical Industry Co., Ltd.) to give 312 mg (yield, 85%) of Compound 45 as white needles.
Melting point: >290 °C (dioxane-water)

Elemental analysis: as $C_9H_{10}N_6O_2 \cdot 0.1C_4H_8O_2$			
Found (%):	C 46.36	H 4.23	N 34.51
Calcd. (%):	C 46.46	H 4.48	N 34.58

IR (KBr) νmax (cm^{-1}) : 1744, 1700, 1649
^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.52(brs, 1H), 11.87(s, 1H), 7.92(s, 1H), 3.94(t, 2H), 1.80-1.60(m, 2H), 0.90(t, 3H)

Example 46

9-Methyl-6-n-propyl-2,3,6,9-tetrahydro-3-thioxo-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 46):

After 800 mg (3.60 mmol) of Compound n prepared in Reference Example 12 was dissolved in 36 ml of pyridine, 3.6 ml of carbon disulfide was added to the solution. The mixture was refluxed for 1.5 hours under heating. After the solvent was evaporated under reduced pressure, 50 ml of toluene was added to the residue. The solvent was reevaporated under reduced pressure, and the residue was tritulated with ether. Recrystallization from acetic acid gave 920 mg (yield, 97%) of Compound 46 as light yellow needles.
Melting point: 275.1-276.8 °C

Elemental analysis: as $C_{10}H_{12}N_6OS \cdot 0.5C_2H_4O_2$			
Found (%):	C 44.87	H 4.63	N 28.52
Calcd. (%):	C 44.89	H 4.79	N 28.55

IR (KBr) νmax (cm^{-1}) : 1726, 1668
^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.96(brs, 1H), 7.93(s, 1H), 3.93(t, 2H), 3.89(s, 3H), 2.00-1.45(m, 2H), 0.90(t, 3H)

Example 47

6-Benzyl-9-methyl-2,3,6,9-tetrahydro-3-thioxo-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 47):

The procedure was performed in a manner similar to Example 46 except for using 1.50 g (5.56 mmol) of Compound p prepared in Reference Example 14. Thus, 1.14 g (yield, 66%) of Compound 47 was obtained as a light yellow powders.
Melting point: 277.5-278.4 °C (dioxane)

Elemental analysis: as $C_{14}H_{12}N_6OS \cdot 0.4C_4H_8O_2 \cdot 0.3H_2O$			
Found (%):	C 53.11	H 4.10	N 23.81
Calcd. (%):	C 53.08	H 4.51	N 23.81

IR (KBr) νmax (cm^{-1}) : 1730, 1673
^{1}H-NMR (DMSO-d_6) δ (ppm) : 7.96(brs, 1H), 7.50-7.15(m, 5H), 5.17(s, 2H), 3.90(s, 3H)
MS (m/e: relative intensity): 312(M^+, 53), 91(100)

Example 48

2-Ethyl-9-methyl-6-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-2,5-dione (Compound 48):

After 1.60 g (6.45 mmol) of Compound 41 prepared in Example 41 was dissolved in 16 ml of N,N-dimethylformamide, 310 mg (7.74 mmol) of 60% sodium hydride was added to the solution under ice cooling. The mixture was stirred for 10 minutes. After 1.55 ml (19.4 mmol) of ethyl iodide was added under ice cooling, the mixture was stirred at 60 °C for 30 minutes. After concentration of the solution, 50 ml of water was added and the mixture was extracted 3 times with 30 ml of chloroform. The extracts were combined and washed with a saturated aqueous sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent: 3% methanol/chloroform) and recrystallized from toluene to give 820 mg (yield, 46%) of Compound 48 as light yellow needles.
Melting point: 238.1-239.7 °C (toluene)

Elemental analysis: as $C_{12}H_{16}N_6O_2 \cdot 0.1H_2O$			
Found (%):	C 51.74	H 5.74	N 30.21
Calcd. (%):	C 51.83	H 5.87	N 30.22

IR (KBr) νmax (cm^{-1}) : 1746, 1696, 1650, 1413
^{1}H-NMR DMSO-d_6) δ (ppm): 7.92(s, 1H), 3.91(t, 2H), 3.88(s, 3H), 3.78(q, 2H), 1.78-1.62(m, 2H), 1.26(t, 3H), 0.89(t, 3H)

Example 49

6-Benzyl-2-ethyl-9-methyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-2,5-dione (Compound 49):

The procedure was performed in a manner similar to Example 48 except for using 1.20 g (4.05 mmol) of Compound 42 obtained in Example 42. Thus, 1.32 g (yield, 100%) of Compound 49 was obtained as white needles.
Melting point: 260.0-261.1 °C (ethanol)

Elemental analysis: as $C_{16}H_{16}N_6O_2 \cdot 0.2H_2O$			
Found (%):	C 58.63	H 4.95	N 25.73
Calcd. (%):	C 58.60	H 5.04	N 25.63

IR (KBr) νmax (cm^{-1}) : 1771, 1755, 1695, 1650
^{1}H-NMR ($CDCl_3$) δ (ppm) : 7.60-7.10(m, 5H), 7.41(s, 1H), 5.22(s, 2H), 3.90(s, 3H), 3.87(q, 2H), 1.32(t, 3H)

Example 50

3-Amino-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 50):

After 756 mg (3.40 mmol) of Compound n obtained in Reference Example 12 was dissolved in 10 ml of methanol, 400 mg (3.75 mmol) of cyanogen bromide was added to the solution. The mixture was refluxed for 2 hours under heating. After the mixture was neutralized with saturated aqueous sodium bicarbonate solution, the precipitates were collected by filtration and washed with water to afford 670 mg (yield, 80%) of Compound 50 as a light yellow powder.
Melting point: >270 °C (decomposed)
IR (KBr) νmax (cm^{-1}): 1698, 1666, 1616, 1323
^{1}H-NMR (90MHz; DMSO-d_6) δ (ppm): 7.85(s, 1H), 6.63(brs, 2H), 3.97(t, 2H), 3.93(s, 3H), 2.00-1.50(m, 2H), 0.91(t, 3H)
MS (m/e; relative intensity): 247(M^+, 100), 205(64), 204(75), 149(23)

Example 51

6-n-Butyl-9-methyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound 51):

1.71 g of Compound 51 as a white powder was obtained (yield, 82%) from 2.0 g (7.94 mmol) of Compound u obtained in Reference Example 19 by the similar method to Example 41.
Melting point: 262.1-264.5° C (acetic acid)

Elemental analysis: as $C_{11}H_{14}N_6O_2$			
Found (%):	C 50.40	H 5.59	N 32.12
Calcd. (%):	C 50.37	H 5.38	N 32.04

IR (KBr) νmax (cm^{-1}) : 1754, 1698, 1652
^{1}H-NMR (DMSO-d_6) δ (ppm) : 11.95(brs, 1H), 7.90(s, 1H), 3.94(t, 2H), 3.86(s, 3H), 1.75-1.60(m, 2H), 1.40-1.25(m, 2H), 0.90(t, 3H)

Reference Example 1

3,7-Dihydro-7-methyl-6-methylthio-3-n-propyl-2H-purin-2-one (Compound a):

In an argon atmosphere, 10.7 g (268 mmol) of 60% sodium hydride was washed with n-hexane 3 times. The solvent was evaporated under reduced pressure and dried. Under ice cooling, 300 ml of N,N'-dimethylformamide was added and a suspension of 28.2 g (134 mmol) of 3-n-propyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86) in 200 ml of N,N'-dimethylformamide was dropwise added to the mixture. The mixture was incubated for 15 minutes, and 25.1 ml (403 mmol) of methyl iodide was dropwise added. After stirring for 30 minutes, 50 ml of ethanol was added to the mixture followed by concentration. Then 250 ml of water was added to the concentrate. The precipitates were collected by filtration to give 25.9 g (yield, 81%) of Compound a .
Melting point: 224.7-226.4° C (acetonitrile)

Elemental analysis: as $C_{10}H_{14}N_4OS$			
Found (%):	C 50.30	H 5.95	N 23.35
Calcd. (%):	C 50.40	H 5.92	N 23.51

IR (KBr) νmax (cm^{-1}) : 1630, 1596, 1557, 1393
^{1}H-NMR ($CDCl_3$) δ (ppm) : 7.53(s, 1H), 4.16(t, 2H), 4.01(s, 3H), 2.71(s, 3H), 1.95-1.77(m, 2H), 0.98(t, 3H)
^{13}C-NMR ($CDCl_3$) δ (ppm): 160.9, 154.7, 151.6, 143.3, 114.3, 45.0, 34.7, 21.2, 12.2, 11.2

Reference Example 2

3,7-Dihydro-6-methylthio-3-n-propyl-2H-purin-2-one (Compound b):

In an argon atmosphere, 9.77 g (244 mmol) of 60% sodium hydride was washed with n-hexane 3 times. The solvent was evaporated under reduced pressure and dried. After 900 ml of N,N'-dimethylformamide was added 57.0 g (271 mmol) of 3-n-propyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86) was gently added under ice cooling. 15 minutes after, 15.2 ml (244 mmol) of methyl iodide was dropwise added to the reaction mixture. After stirring for 30 minutes, 50 ml of ethanol was added and the mixture was concentrated under reduced pressure. Then 400 ml of water was added

and precipitates were collected by filtration to give 13.9 g (yield, 23%) of Compound b as light yellow powder. The filtrate was extracted 5 times with 200 ml of chloroform. After washing with a saturated aqueous sodium chloride solution, the extract was dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% methanol/chloroform) to give further 16.0 g (yield, 26%) of Compound b as a light yellow powder.
Melting point: 240.8-242.5 °C
IR (KBr) νmax (cm^{-1}) : 3400(br), 1600, 1588, 1572
^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.54(brs, 1H), 8.13(brs, 1H), 3.99(t, 2H), 2.57(s, 3H), 1.80-1.62(m, 2H), 0.88(t, 3H)
^{13}C-NMR DMSO-d_6) δ (ppm): 11.0, 11.3, 20.6, 44.4, 112.8(br), 141.9(br), 149.4(br), 153.8, 160.6(br)
MS (m/e; relative intensity): 224(M^+, 36), 195(13), 182(100), 135(43)

Reference Example 3

8-Cyclopentyl-3-n-propylxanthine (Compound c):

After 30 g (163 mmol) of 5,6-diamino-1-propyl-2,4-(1H,3H)-pyrimidinedione (Japanese Published Unexamined Patent Application No. 57517/80) was suspended in 600 ml of N,N-dimethylformamide, 17.7 ml (163 mmol) of cyclopentanecarboxylic acid, 30.0 g (196 mmol) of hydroxybenztriazole and 50.5 g (245 mmol) of dicyclohexylcarbodiimide were added to the suspension. The mixture was stirred at room temperature overnight. After insoluble materials were filtered off, the filtrate was evaporated under reduced pressure. To the residue was added 600 ml of 4 N sodium hydroxide aqueous solution and the solution was refluxed for 10 minutes under heating. After ice cooling, insoluble materials were filtered off and 50 ml of methanol was added. The resulting mixture was neutralized with conc. hydrochloric acid. The precipitates were collected by filtration to afford 28.3 g (yield, 66%) of Compound c as a white powder.
Melting point: 311.3-313.1 °C (dimethylformamide)

Elemental analysis: as $C_{13}H_{18}N_4O_2$			
Found (%):	C 59.56	H 6.96	N 21.69
Calcd. (%):	C 59.52	H 6.92	N 21.36

IR (KBr) νmax (cm^{-1}) : 3150, 2880, 1698, 1669
^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.05(brs, 1H), 10.94(s, 1H), 3.86(t, 2H), 3.18-3.04(m, 1H), 2.05-1.55(m, 10H), 0.87(t, 3H)
^{13}C-NMR (DMSO-d_6) δ (ppm): 157.7, 154.3, 150.9, 149.4, 106.5, 43.3, 39.0, 31.9, 25.0, 20.9, 10.9

Reference Example 4

8-Cyclopentyl-3-n-propyl-6-thioxanthine (Compound d):

14.1 g (53.8 mmol) of Compound c obtained in Reference Example 3 and 19.5 g (87.7 mmol) of phosphorous pentasulfide in 280 ml of pyridine was refluxed for 4 hours under heating. The reaction mixture was poured onto 600 ml of ice water and the precipitates were collected by filtration. The filtrate was concentrated under reduced pressure and the precipitates were taken out by filtration. The collected precipitates were combined and 400 ml of 2 N sodium hydroxide aqueous solution was added to remove insoluble matters. After neutralization with conc. hydrochloric acid, the precipitates were collected by filtration to give crude Compound d . The crude product was recrystallized from ethanol-water to give 13.5 g (yield, 90%) of Compound d as a light yellow plate.
Melting point: 214.3-215.9 °C

Elemental analysis: as $C_{13}H_{18}N_4OS \cdot 1/4C_2H_5OH$			
Found (%):	C 56.17	H 6.76	N 19.44
Calcd. (%):	C 55.93	H 6.78	N 19.33

IR (KBr) νmax (cm^{-1}) : 2960, 1663, 1605, 1510, 1403
^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.03(brs, 1H), 12.04(brs, 1H), 3.90(t, 2H), 3.30-3.10(m, 1H), 2.05-1.55(m, 10H), 0.87(t, 3H)
^{13}C-NMR (DMSO-d_6) δ (ppm): 173.3, 161.5, 148.9, 145.7, 118.5, 56.0, 43.8, 38.7, 32.0, 25.2, 20.7, 18.5, 10.9

Reference Example 5

8-Cyclopentyl-3,7-dihydro-6-methylthio-3-n-propyl-2H-purin-2-one (Compound e):

The procedure was performed in a manner similar to Reference Example 2 except for using 6.00 g (21.6 mmol) of Compound d obtained in Reference Example 4. Thus, 4.70 g (yield, 75%) of Compound e was obtained as light yellow needles.
Melting point: 257.5-259.2 °C

Elemental analysis: as $C_{14}H_{20}N_4OS$			
Found (%):	C 57.77	H 7.22	N 19.36
Calcd. (%):	C 57.51	H 6.89	N 19.16

IR (KBr) νmax (cm^{-1}) : 1599, 1580, 1553, 1513
^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm) : 4.24(t, 2H), 3.53-3.15(m, 1H), 2.10(s, 3H), 2.50-1.50(m, 10H), 0.95(t, 3H)

Reference Example 6

7-Benzyloxymethyl-3,7-dihydro-6-methylthio-3-n-propyl-2H-purin-2-one (Compound f):

After 224 mg (1.0 mmol) of Compound b obtained in Reference Example 2 was dissolved in 2 ml of N,N'-dimethylformamide, 48.0 mg (1.2 mmol) of 60% sodium hydride was added to the mixture under ice cooling. 15 minutes after, 209 µl (1.5 mmol) of benzyl chloromethyl ether was added to the mixture. The mixture was stirred for an hour, poured onto 10 ml of water, and extracted 3 times with 5 ml of chloroform. After washing with a saturated aqueous sodium chloride solution, the extracts were dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was triturated with ether to give 223 mg (yield, 65%) of Compound f as a white powder.
Melting point: 166.8-168.3 °C

Elemental analysis: as $C_{17}H_{20}N_4O_2S$			
Found (%):	C 58.99	H 5.80	N 16.22
Calcd. (%):	C 59.28	H 5.85	N 16.27

IR (KBr) νmax (cm^{-1}) : 1623, 1592, 1556
^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm) : 7.58(s, 1H), 7.29(s, 5H), 5.81(s, 2H), 4.59(s, 2H), 4.12(t, 2H), 2.70(s, 3H), 2.00-1.60(m, 2H), 0.99(t, 3H)
MS (m/e; relative intensity): 344(M^+, 19), 302(9), 211(10), 181(10), 91(100)

Reference Example 7

3-Benzyl-6-thioxanthine (Compound g):

The procedure was performed in a manner similar to Reference Example 4 except for using 31.0 g (128 mmol) of 3-benzylxanthine [Biochemistry, 16 , 3316 (1977)]. Thus, 28.7 g (yield, 87%) of Compound g was obtained as a light yellow powder.
Melting point: 261.8-263.1 °C (DMSO-water)
IR (KBr) νmax (cm^{-1}) : 1682, 1600, 1560, 1426
^{1}H-NMR (90MHz; DMSO-d_6) δ (ppm) : 13.4(brs, 1H), 12.2(brs, 1H), 7.99(s, 1H), 7.50-7.05(m, 5H), 5.12(s, 2H)

Reference Example 8

3-Benzyl-3,7-dihydro-7-methyl-6-methylthio-2H-purin-2-one (Compound h) and 3-benzyl-3,7-dihydro-6-methylthio-2H-purin-2-one (Compound i):

The procedure was performed in a manner similar to Reference Example 2 except for using 14 g (54.3 mmol) of Compound g obtained in Reference Example 7. The crude product was purified by silica gel column chromatography and a product was eluted with 5% methanol/chloroform. Concentration of the elution (5% methanol/chloroform) gave 5.86 g (yield, 40%) of Compound h as a light yellow powder.
Melting point: 268.1-269.8 °C

Elemental analysis: as $C_{13}H_{12}N_4OS$			
Found (%):	C 57.42	H 4.13	N 20.14
Calcd. (%):	C 57.34	H 4.44	N 20.57

IR (KBr) νmax (cm^{-1}) : 3420(br), 1600, 1566, 1543
^{1}H-NMR (90MHz; DMSO-d_6) δ (ppm) : 13.50(brs, 1H), 8.07(s, 1H), 7.45-7.05(m, 5H), 5.22(s, 2H), 2.60(s, 3H)
MS (m/e: relative intensity): 272(M^+, 53), 257(11), 225(18), 91(100), 65(18)

Concentrating of the elution (2% methanol/chloroform) fraction eluted by silica gel column chromatography afforded 7.24 g of the residue. The procedure was performed in a manner similar to Reference Example 1 except that 7.24 g of the residue was used. Thus, 5.13 g (yield, 33%) of Compound i was obtained as a light yellow powder.
Melting point: 214.8-216.4 °C
IR (KBr) νmax (cm^{-1}) : 1633, 1591. 1558
^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm) : 7.47(s, 1H), 7.60-7.05(m, 5H), 5.32(s, 2H), 3.82(s, 3H), 2.67(s, 3H)
MS (m/e: relative intensity): 286(M^+, 97), 271(40), 228(50),211(17), 195(19), 91(100)

Reference Example 9

3-Phenyl-6-thioxanthine (Compound j):

The procedure was performed in a manner similar to Reference Example 4 except for using 23.8 g (104 mmol) of 3-phenylxanthine [Chem. Pharm. Bull., 14 , 1365 (1966)]. Thus, 19.9 g (yield, 78%) of Compound j was obtained as a light yellow powder.
Melting point: >290 °C
IR (KBr) νmax (cm^{-1}) : 1682, 1595, 1587, 1415
^{1}H-NMR (90MHz; DMSO-d_6) δ (ppm) : 7.94(s, 1H), 7.60-7.30(m, 5H)

Reference Example 10

3,7-Dihydro-7-methyl-6-methylthio-3-phenyl-2H-purin-2-one (Compound k) and 3,7-dihydro-9-methyl-6-methylthio-2H-purin-2-one (Compound l):

The procedure was performed in a manner similar to Reference Example 1 except for using 9.89 g (40.5 mmol) of Compound g obtained in Reference Example 7. The crude product was purified by silica gel column chromatography (eluent: 1% methanol/chloroform). Thus, 7.75 g (yield, 74%) of Compound k and 1.62 g (yield, 16%) of Compound l were obtained as a light yellow powder.

Physicochemical properties of Compound k are as follows.

Rf: 0.55 [TLC plate: silica gel $60F_{254}$ (layer thickness of 0.25 mm, manufactured by Merck), developing solvent: 10% methanol/chloroform]

Melting point: 261.1-262.8 °C

IR (KBr) νmax (cm^{-1}) : 1640, 1571, 1555

^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm) : 7.48(s, 1H), 7.60-7.30(m, 5H), 4.01(s, 3H), 2.75(s, 3H)

Physicochemical properties of Compound l are as follows.

Rf: 0.46 [TLC plate: silica gel $60F_{254}$ (layer thickness of 0.25 mm, manufactured by Merck), developing solvent: 10% methanol/chloroform]

IR (KBr) νmax (cm^{-1}) : 1660, 1556, 1371

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.62-7.50(m, 3H), 7.45-7.37(m, 2H), 7.27(s, 1H), 2.94(s, 3H), 2.69(s, 3H)

^{13}C-NMR ($CDCl_3$) δ (ppm): 171.2, 153.8, 139.6, 138.8, 135.2, 130.1, 130.0, 129.1, 122.2, 33.0, 11.9

MS (m/e: relative intensity): 272(M^+, 96), 225(88), 198(14), 104(17), 77(28), 42(100)

Reference Example 11

3-Benzyl-7-benzyloxymethyl-3,7-dihydro-6-methylthio-2H-purin-2-one (Compound m):

The procedure was performed in a manner similar to Reference Example 4 except that 7.00 g (25.7 mmol) of Compound f obtained in Reference Example 6 was used.

Thus, 9.15 g (yield, 91%) of Compound m was obtained as a white powder.

Melting point: 193.7-195.2 °C

IR (KBr) νmax (cm^{-1}) : 1641, 1625, 1586. 1555

^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm) : 7.59(s, 1H), 7.65-7.15(m, 10H), 5.60(s, 2H), 5.36(s, 2H), 4.58(s, 2H), 2.69-(s, 3H)

Reference Example 12

3,7-Dihydro-6-hydrazino-7-methyl-3-n-propyl-2H-purin-2-one (Compound n):

After 50 ml of hydrazine monohydrate was added to 5.00 g (21.0 mmol) of Compound a prepared in Reference Example 1, the mixture was stirred at room temperature for 2 days. The precipitates were collected by filtration and washed with isopropanol to give 4.04 g (yield, 87%) as a white powder.

Melting point: 180.1-181.9 °C

IR (KBr) νmax (cm^{-1}) : 1673

^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm) : 7.25(s, 1H), 3.92(t, 2H), 3.87(s, 3H), 2.00-1.55(m, 2H), 0.97(t, 3H)

MS (m/e: relative intensity): 222(M^+, 100), 193(13), 180(49), 179(22)

Reference Example 13

3,7-Dihydro-3,7-di-n-propyl-6-methylthio-2H-purin-2-one (Compound o):

2.00 g (8.93 mmol) of Compound b obtained in Reference Example 2 was gently added to a suspension of 356 mg (8.93 mmol) of 60% sodium hydride in 20 ml of N,N-dimethylformamide at 0 °C. 10 minutes after, 2.64 ml (27.0 mmol) of propyl iodide was gently added to the mixture. The mixture was stirred at

room temperature for 2 hours and a half. After 150 ml of saturated ammonium chloride aqueous solution was added to the reaction solution, the mixture was extracted 3 times with chloroform. The extracts were combined and washed twice with a saturated aqueous sodium chloride. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. 50% ether/n-hexane was added to the residue. The precipitates were taken out by filtration to give 2.09 g (yield, 84%) of Compound o as a light yellow powder.

^{1}H-NMR ($CDCl_3$) δ (ppm) : 7.53(s, 1H), 4.22(t, 2H), 4.14(t, 2H), 2.70(s, 3H), 2.20-1.65(m, 4H), 1.15-0.90(m, 6H)

Reference Example 14

3-Benzyl-3,7-dihydro-6-hydrazino-7-methyl-2H-purin-2-one (Compound p):

After 16.0 ml of hydrazine hydrate was added to 2.00 g (6.99 mmol) of Compound h prepared in Reference Example 8, the mixture was stirred at room temperature for day and night. The reaction mixture was poured onto 300 ml of water and the precipitates were taken out by filtration and washed with ether to give 1.60 g (yield, 85%) of Compound p as a white powder.

Melting point: 180.0-181.9 °C

MS (m/e; relative intensity): 222(M^+, 100), 180(52)

^{1}H-NMR DMSO-d_6) δ (ppm): 7.78(s, 1H), 7.50-7.10(m, 5H), 5.03(s, 2H), 3.80(s, 3H)

Reference Example 15

3-n-Butyl-3,7-dihydro-6-methylthio-2H-purin-2-one (Compound q)

7.88 g of Compound q (yield, 41%) was obtained from 18.2 g (81.0 mmol) of 3-n-butyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86, by the similar method to Reference Example 2 as a yellow powder.

Elemental analysis: as $C_{16}H_{14}N_4OS$			
Found (%):	C 50.22	H 6.02	N 23.67
Calcd. (%):	C 50.40	H 5.92	N 23.51

NMR (DMSO-d_6; 90MHz) δ (ppm): 8.05(s, 1H), 4.00(t, 2H), 2.56(s, 3H), 1.85-1.05(m, 4H), 0.89(t, 3H)

MS (m/e: relative intensity): 238(M^+, 38), 196(100), 182(73), 135(60)

Reference Example 16

7-Benzyloxymethyl-3-n-butyl-3,7-dihydro-6-methylthio-2H-purin-2-one (Compound r):

4.83 g of Compound r (yield, 85%) as a white powder was obtained from 3.78 g (15.9 mmol) of Compound q in Reference Example 15, by the method similar to Reference Example 6.

^{1}H-NMR ($CDCl_3$: 90MHz) δ (ppm): 7.58(s, 1H), 7.28(brs, 5H), 5.60(s, 2H), 4.59(s, 2H), 4.17(t, 2H), 2.70(s, 3H), 1.90-1.15(m, 4H), 0.95(t, 3H)

MS (m/e: relative intensity): 358(M^+, 14), 316(26), 91(100)

Reference Example 17

7-Benzyl-6-benzylthio-3,7-dihydro-3-n-propyl-2H-purin-2-one (Compound s)

8.30 g of Compound s (yields 89%) as a white powder was obtained from 5.00 g (23.8 mmol) of 3-n-propyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86) and 7.08 ml (59.5 mmol) of benzyl bromides, by the similar manner to Reference Example 1.
^{1}H-NMR ($CDCl_3$; 90MHz) δ (ppm): 7.48(s, 1H), 7.50-7.00(m, 10H), 5.41(s, 2H), 4.60(s, 2H), 4.16(t, 2H), 2.05-1.60(m, 2H), 1.00(t, 3H)

Reference Example 18

3,7-Dihydro-3,7-di-n-propyl-6-n-propylthio-2H-purin-2-one (Compound t)

3.15 g of Compound t (yield, 75%) as a light yellow powder was obtained from 3.00 g (14.3 mmol) of 3-n-propyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86) and 3.49 ml (35.7 mmol) of propyliodide, by similar manner to Reference Example 1.
^{1}H-NMR ($CDCl_3$; 90MHz) δ (ppm): 7.55(s, 1H), 4.30-4.00(m, 4H), 3.38(t, 2H), 2.15-1.55(m, 6H), 1.20-0.85(m, 9H)

Reference Example 19

3-n-Butyl-3,7-dihydro-7-methyl-6-methylthio-2H-purin-2-one (Compound u):

6.33 g of Compound u (yield, 52%) as a light yellow powder was obtained from 10.7 g (47.9 mmol) of 3-n-butyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86), by the similar method to Reference Example 1.
^{1}H-NMR ($CDCl_3$; 90MHz) δ (ppm): 7.50(s, 1H), 4.18(t, 2H), 3.98(s, 3H), 2.68(s, 3H), 1.95-1.20(m, 4H), 0.93(t, 3H)
MS (m/e; relative intensity): 252(M^+, 38), 210(100), 196(68)

Pharmaceutical preparation 1

Tablet:

A tablet having the following composition was prepared according to the conventional method.

Compound 25	20 mg
Lactose	60 mg
Potato starch	30 mg
Polyvinyl alcohol	3 mg
Magnesium stearate	1 mg

Pharmaceutical preparation 2

Powder:

A powder having the following composition was prepared according to the conventional method.

Compound 31	20 mg
Lactose	300 mg

Pharmaceutical preparation 3

Syrup:

A syrup having the following composition was prepared according to the conventional method.

Compound 41	20 mg
Refined saccharose	30 mg
Ethyl p-hydroxybenzoate	40 mg
Propyl p-hydroxybenzoate	10 mg
Strawberry flavor	0.1 ml
Water to make the total valume	100 ml

Pharmaceutical preparation 4

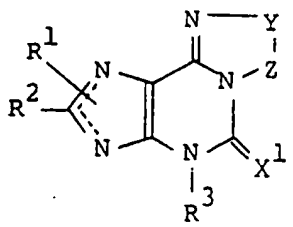
Capsule:

Ingredients set forth below were admixed and charged into gelatin capsules in accordance with the conventional method to thereby prepare a capsule.

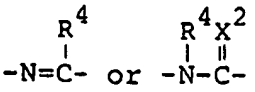
Compound 51	20 mg
Lactose	200 mg
Magnesium stearate	5 mg

Claims

1. An s-triazolo[3,4-i]purine compound represented by the formula:



wherein Y-Z represents



where R^4 represents hydrogen, alkyl, a substituted or unsubstituted aromatic heterocyclic group or substituted or unsubstituted aryl; and X^2 represents oxygen, sulfur or NH;
each of R^1 and R^2 independently represents hydrogen, alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl;
R^3 represents alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl;
X^1 represents oxygen or sulfur;
and

represents a single bond or a double bond or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein Y-Z represents

3. A compound according to Claim 2, wherein R^4 is a substituted or unsubstituted aromatic heterocyclic group; each of R^1 and R^2 independently represents hydrogen, alkyl, cycloalkyl or aralkyl; R^3 represents alkyl or aralkyl; and X^1 is oxygen.

4. A compound according to Claim 3, wherein R^4 is unsubstituted or substituted pyridyl.

5. A compound according to Claim 4, which is selected from the group consisting of
6,9-dihydro-9-methyl-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
6,9-dihydro-9-methyl-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
6,9-dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
6,9-dihydro-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
6-benzyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
6-n-butyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
9-benzyl-6,9-dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one; and
6,9-dihydro-6,9-di-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one.

6 . A compound according to Claim 1, wherein Y-Z represents

7. A compound according to Claim 6, wherein R^4 is hydrogen or alkyl; X^2 is oxygen; each of R^1 and R^2 independently represents hydrogen, alkyl or cycloalkyl; R^3 is alkyl; and X^1 is oxygen.

8. A compound according to Claim 7, which is 9-methyl-6-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]-purin-3,5-dione or 6-n-butyl-9-methyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione.

9. A compound according to Claim 1, wherein said salt is selected from the group consisting of pharmaceutically acceptable acid addition salt, metal salt, ammonium salt, organic amine addition salt and amino acid addition salt.

10. A pharmaceutical composition comprising a pharmaceutical carrier and as an active ingredient, an effective amount of the compound as defined by Claim 1.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 417 790 A3**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 90117662.8

(22) Date of filing: 13.09.90

(51) Int. Cl.5: C07D 487/14, A61K 31/52, A61K 31/505, //(C07D487/14, 249:00,239:00,235:00)

(30) Priority: 14.09.89 JP 239117/89
06.10.89 JP 261761/89

(43) Date of publication of application:
20.03.91 Bulletin 91/12

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(88) Date of deferred publication of the search report:
18.03.92 Bulletin 92/12

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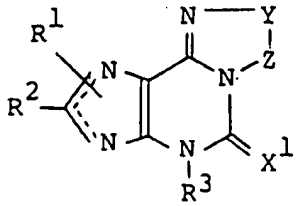
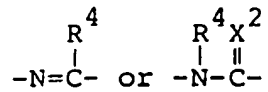
(54) S-triazolo[3,4-i]purine derivatives.

(57) There are disclosed s-triazolo[3,4-i]purine derivatives represented by formula:



wherein Y-Z represents



where R^4 represents hydrogen, alkyl, substituted or unsubstituted aromatic heterocyclic group or substituted or unsubstituted aryl; and X^2 represents oxygen, sulfur or NH; each of R^1 and R^2 independently represents hydrogen, alkyl, cycloalkyl, aralkyl or

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substituted or unsubstituted aryl; R^3 represents alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl; X^1 represents oxygen or sulfur; and

represents a single bond or a double bond or pharmaceutically acceptable salts thereof.

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EUROPEAN SEARCH REPORT

Application Number

EP 90117662.8

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	US - A - 4 404 380 (D.L. TEMPLE, JR.) * Column 4, line 56 - column 48 * --	1,10	C 07 D 487/14 A 61 K 31/52 A 61 K 31/505// (C 07 D 487/14 C 07 D 249/00 C 07 D 239/00 C 07 D 235/00)
A	CHEMICAL ABSTRACTS, vol. 98, no. 3, January 17, 1983 Columbus, Ohio, USA D.J. BROWN et al. "3-(Alkylthio)-s-triazolo(3-4-i)-purines and 9-alylbis-s--triazolo(3,4-b:3',4'-i)-purines." page 507, abstract-no. 16 636w	1	
D	& Aust. J. Chem 1982, 35(6), 1263-7 --		
A	CHEMICAL ABSTRACTS, vol. 63, no. 13, December 20, 1965 Columbus, Ohio, USA C. TEMPLE, JR. et al. "Cyclization of 6-hydrazinopurines to s-triazolo(3,4-i)-purines and their rearrangement to the isomeric s-triazolo(5,1,-i)purines." abstract-no. 18084h-18085a, line 3	1	
	& J. Org. Chem. 30(11), 3601-3 (1965) ----		

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 D 487/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	23-01-1992	HOFBAUER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 417 790 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
04.12.1996 Bulletin 1996/49

(21) Application number: **90117662.8**

(22) Date of filing: **13.09.1990**

(51) Int Cl.[6]: **C07D 487/14**, A61K 31/52, A61K 31/505 // (C07D487/14, 249:00, 239:00, 235:00)

(54) S-triazolo[3,4-i]purine derivatives

5-Triazolo(3,4-i)purinderivate

Dérivés du S-triazolo[3,4-i]purine

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(30) Priority: **14.09.1989 JP 239117/89**
06.10.1989 JP 261761/89

(43) Date of publication of application:
20.03.1991 Bulletin 1991/12

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(56) References cited:
US-A- 4 404 380

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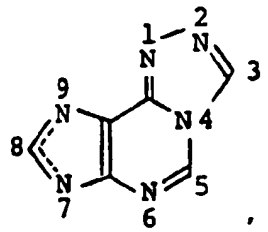
EP 0 417 790 B1

Printed by Jouve, 75001 PARIS (FR)

Description

The present invention relates to novel s-triazolo-[3,4-i]purine derivatives which possess a broncho-dilatory activity, diuretic activity, renal protecting activity and/or anti-amnestic activity.

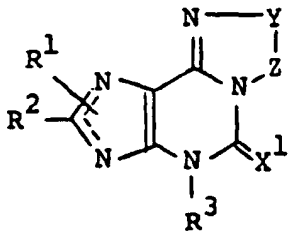
As s-triazolo[3,4-i]purine derivatives represented by the following formula :



9H-s-triazolo[3,4-i]purine which has no substituents at the 3-, 5-, 7- and 8-positions and s-triazolo[3,4-i]purine derivatives which have benzyl at the 7- or 9-position are disclosed in J. Org. Chem., 30, 3601 (1965); and 3-alkylthio-s-triazolo [3,4-i]purine having SH, SCH_3 or SCH_2CONH_2 at the 3-position is disclosed in Aust. J. Chem., 35, 1263 (1982). As yet their pharmacological activities are unknown. Imidazo [1,2-a]purine derivatives are known from US-A-4,404,380 and certain s-triazolo [3,4-i]purines are disclosed in CA 63:18084h wherein a publication in J. Org. Chem. 30(11), 3601 (1965) is cited. However, s-triazolo [3,4-i]purine derivatives having a substituent at the 5-position thereof have not been reported so far.

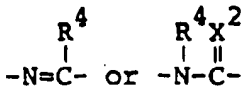
An object of the present invention is to provide novel s-triazolo[3,4-i]purine derivatives having an broncho-dilatory effect, anti-asthmatic effect, diuretic effect, renal protecting effect and/or anti-amnestic effect.

The present invention is directed to s-triazolo-[3,4-i]purine derivatives represented by formula (I):



(I)

wherein Y-Z represents



where R^4 represents hydrogen, alkyl, an aromatic heterocyclic group which is optionally substituted with 1 or 2 substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen, or substituted or unsubstituted aryl; and X^2 represents oxygen, sulfur or NH;

each of R^1 and R^2 independently represents hydrogen, alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl;
R^3 represents alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl;
X^1 represents oxygen or sulfur;
--- represents a single bond or a double bond and substituted or unsubstituted aryl means aryl which is optionally substituted with 1 or 2 substituents independently selected from C_1-C_6 alkyl, trifluoromethyl, hydroxyl, C_1-C_6

alkoxyl, C_1-C_6 alkylthio, nitro, halogen, amino, C_1-C_6 alkylamino, C_1-C_6 alkanoylamino, aroylamino, carboxyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyl and aroyl or pharmaceutically acceptable salts thereof.

In the definitions of the groups in formula (I), the alkyl means a straight or branched alkyl having 1 to 10 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc. The cycloalkyl includes an alicyclic alkyl having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, etc. The aralkyl includes aralkyls having 7 to 15 carbon atoms such as benzyl, phenethyl, benzhydryl, etc. The aryl includes aryls having 6 to 10 carbon atoms such as phenyl, naphthyl, etc. The aromatic heterocyclic group includes heterocyclic rings of 5- or 6-members such as thienyl, furyl, pyrazolyl, oxazolyl, imidazolyl, pyridyl, etc.

The C_1-C_6 alkyl and the alkyl moiety in the C_{1-6} alkoxyl, C_1-C_6 alkylthio, C_1-C_6 alkylamino and C_1-C_6 alkoxycarbonyl mean a straight or branched alkyl having 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl.

The C_1-C_6 alkanoyl and the alkanoyl moiety in the C_1-C_6 alkanoylamino include alkanoyl having 1 to 6 carbon atoms such as formyl, acetyl, propionyl, butyryl, isobutyl, pivaloyl, valeryl, isovaleryl, etc.

The aroyl and the aroyl moiety in the aroylamino include, for example, benzoyl, toluyl, propylbenzoyl, naphthoyl, etc.

The halogen means fluorine, chlorine, bromine and iodine.

The salts of Compound (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, amino acid addition salts, etc.

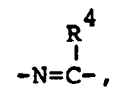
The pharmaceutically acceptable acid addition salts of Compound (I), include inorganic acid salt such as hydrochloride, sulfate, phosphate, etc. and organic acid salts such as acetate, maleate, fumarate, tartrate, citrate, etc. The pharmaceutically acceptable metal salts include alkali metal salts such as sodium salt, potassium salt etc.; alkaline earth metal salts such as magnesium salt, calcium salt, etc. and further an aluminum salt and a zinc salt. The pharmaceutically acceptable organic amine addition salts include addition salt of morpholine, piperidine, etc. The pharmaceutically acceptable amino acid addition salts, include lysine, glycine, phenylalanine, etc.

The methods for preparing Compound (I) are described below.

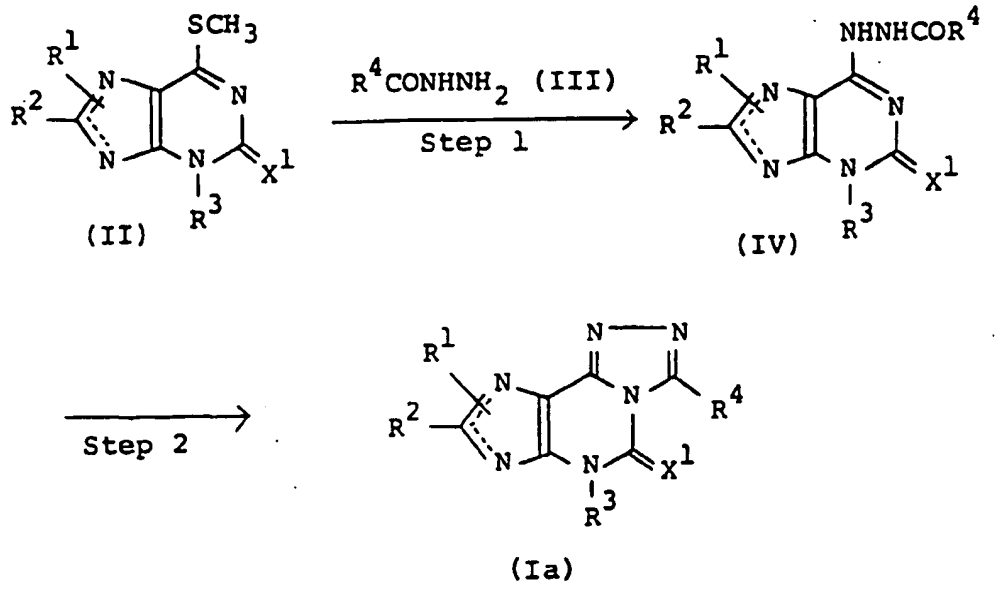
When the defined groups are changed under the conditions of the following processes or are inadequate to proceeding of the following processes, processes can be readily carried out by a usual method in the organic synthetic chemistry, for example, by protection of functional groups, elimination of protecting groups.

Process 1

Compound (Ia), which is Compound (I) where Y-Z is



is synthesized according to Steps 1 and 2.



wherein X^1, R^1, R^2, R^3 and R^4 have the same significance as described above.

(Step 1)

Compound (IV) is obtained by reacting Compound (II) with Compound (III).

Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; ketones such as acetone, methyl ethyl ketone, etc.; aromatic hydrocarbons such as toluene, xylene, etc.; halogenated hydrocarbons such as dichloroethane, 1,1,2,2-tetrachloroethane, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination. The reaction is performed at 50 to 200°C and completed in 10 minutes to 72 hours.

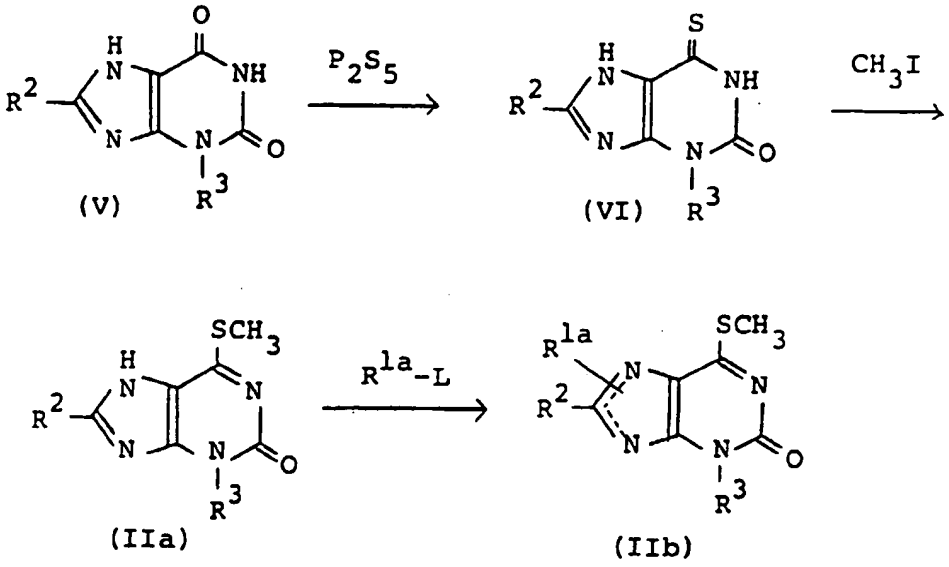
(Step 2)

Compound (Ia) is obtained by cyclization of Compound (IV). The reaction is performed in a solvent in the presence of an acid catalyst.

The acid catalyst includes, for example, hydrochloric acid, sulfuric acid, sulfonic acid such as p-toluenesulfonic acid, camphor sulfonic acid, etc., or silica gel powders. The acid catalyst is used alone or in combination.

Any solvent is used so long as it is inert to the reaction. The solvent includes aromatic hydrocarbons such as toluene, xylene, etc.; halogenated hydrocarbons such as dichloroethane, 1,1,2,2-tetrachloroethane, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination. The reaction is performed at 50 to 150°C and completed in 10 minutes to 4 hours.

Compounds (IIa) and (IIb), among the starting Compound (II) wherein X^1 is oxygen is prepared by the method of Kleiner et al. [J. Chem. Soc., Perkin I, 739 (1973)] or by a modified method of Kleiner et al. The reaction steps are illustrated as follows.



wherein R^{1a} represents a group other than hydrogen in the definition for R^1 described above; R^2 and R^3 have the same significance as described above; and L represents a leaving group.

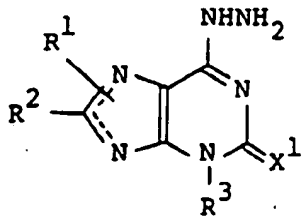
The leaving group denoted by L includes, for example, halogen atom such as chlorine, bromine, iodine, etc.; alkylsulfonyloxy such as methanesulfonyloxy, etc.; arylsulfonyloxy such as phenylsulfonyloxy, p-toluenesulfonyloxy, etc.

Compound (V) in step 2 is synthesized by a notorious method [Biochemistry, 16, 3316 (1977)] or its modified method.

The starting Compound (IIC), which is Compound (II) where X^1 is sulfur is synthesized by the method of Jacobson et al. [J. Med. Chem., 32, 1873 (1989)] or by a modified method of Jacobson et al.

Process 2

Compound (Ia) is also synthesized by reacting Compound (VII) with Compound (VIII). The reaction is performed in the presence or absence of solvent.



(VII)

(wherein X^1, R^1, R^2 and R^3 have the same significance as described above.)

$$R^4C(OR^5)_3 \qquad \text{(VIII)}$$

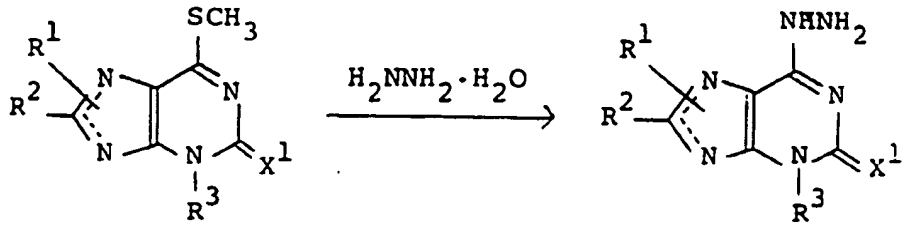
(wherein R^4 has the same significance as described above and R^5 represents alkyl having 1 to 10 carbon atoms.)

Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, ethers such as tetrahydrofuran, dioxane, etc.; dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; alcohols such as methanol, ethanol, isopropyl alcohol, etc.; halogenated hydrocarbons such as dichloroethane, 1,1,2,2-tetrachlo-

roethane, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination.

The reaction is performed at 50 to 150°C and completed in 10 minutes to 4 hours.

The starting Compound (VII) is prepared from Compound (II) according to a modification of the notorious method as described in I1 Farmaco Ed. Sci., 40, 221 (1985). The reaction is performed as follows.



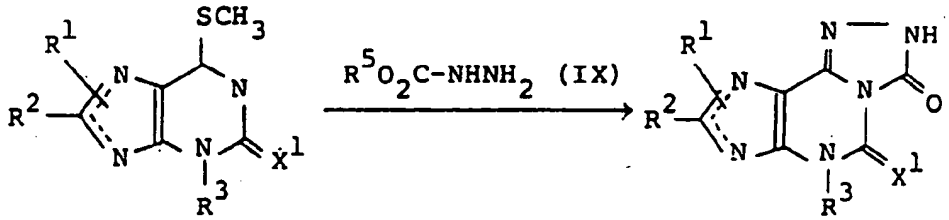
(II) (VII)

(wherein X^1, R^1, R^2 and R^3 have the same significance as described above.)

Process 3

Compound (Ib1) which is Compound (I) wherein Y-Z is

is synthesized according to the following step.



(II) (Ib1)

(wherein R^1, R^2, R^3, R^5 and X^1 have the same significance as described above.)

Compound (Ib1) is obtained by reacting Compound (II) with Compound (IX).

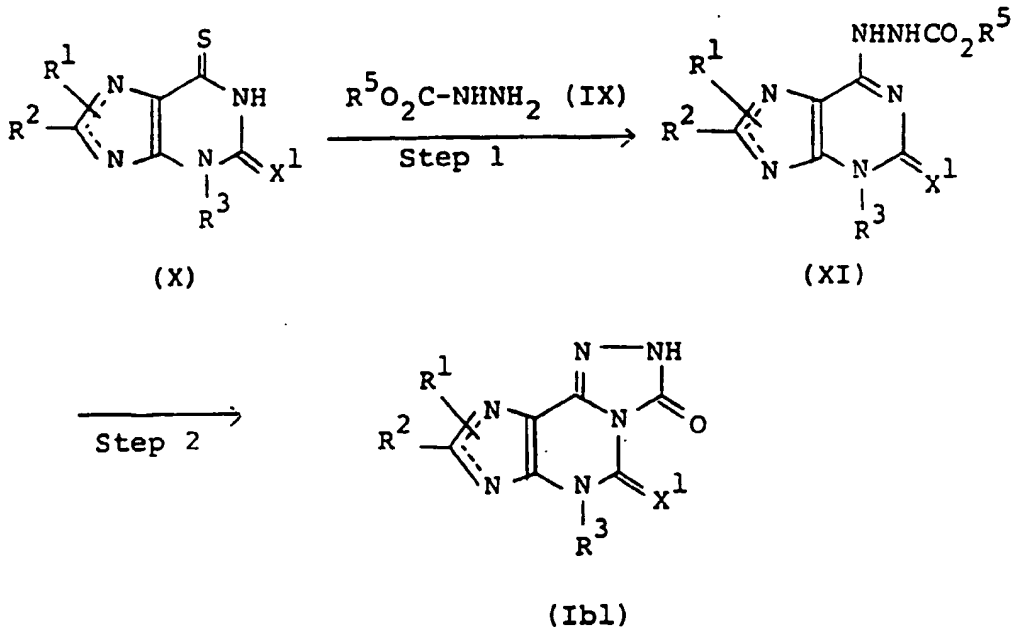
Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; ketones such as acetone, methyl ethyl ketone, etc.; aromatic hydrocarbons such as toluene, xylene, etc.; halogenated hydrocarbons such as dichloroethane, 1,1,2,2-tetrachloroethane, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination. The reaction is performed at 50 to 200°C and completed in 10 minutes to 12 hours.

The starting Compound (II) is obtained by the process shown in Process 1.

The starting Compound (IX) is commercially available.

Process 4

Compound (Ib1) is also synthesized by the following steps:



(X) (XI) (Ibl)

(wherein R^1, R^2, R^3, R^5 and X^1 have the same significance as described above.)

(Step 1)

Compound (XI) is obtained by reacting Compound (X) with Compound (IX).

Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; alcohols such as methanol, ethanol, n-butanol, etc.; ketones such as acetone, methyl ethyl ketone, etc.; aromatic hydrocarbons such as toluene, xylene, etc.; halogenated hydrocarbons such as dichloroethane, 1,1,2,2-tetrachloroethane, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination.

The reaction is carried out at 50 to 200°C and completed in 1 to 48 hours.

The starting Compound (Xa), which is Compound (X) wherein X^1 is oxygen can be prepared by the method of Reichman et al. [J. Chem. Soc., Perkin I, 2647 (1973)] or, by the method of Woodridge et al. [J. Chem. Soc., 1863 (1962)] or by a modification of these methods.

The starting Compound (Xb), which is Compound (X) wherein X^1 is sulfur can be prepared by the method of Jacobson et al. [J. Med. Chem., 32, 1873 (1989)] or by a modified method of Jacobson et al.

(Step 2)

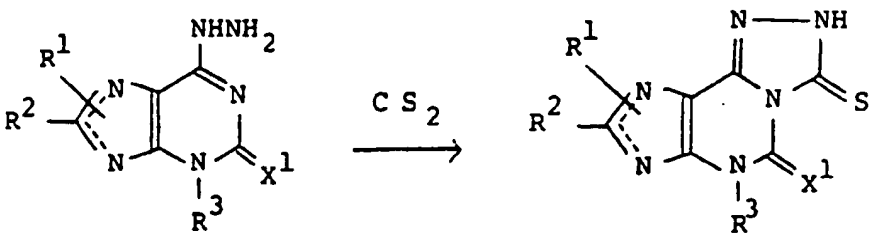
Compound (Ib1) is obtained by cyclization of Compound (XI). The reaction is performed under heating in the presence or absence of a solvent. Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; alcohols such as methanol, ethanol, n-butanol, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination.

The reaction is carried out at 100 to 200°C and completed in 1 to 24 hours.

Process 5

Compound (Ib2) which is Compound (I) wherein Y-Z is

is synthesized by the following step.



(VII) (Ib2)

(wherein R^1, R^2, R^3 and X^1 have the same significance as described above.)

Compound (Ib2) can be synthesized by reacting Compound (VII) with carbon disulfide in the presence of or absence of a solvent. Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, pyridines such as pyridine, quinoline, etc.; dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; dimethylsulfoxide, etc. The solvent is used alone or in combination.

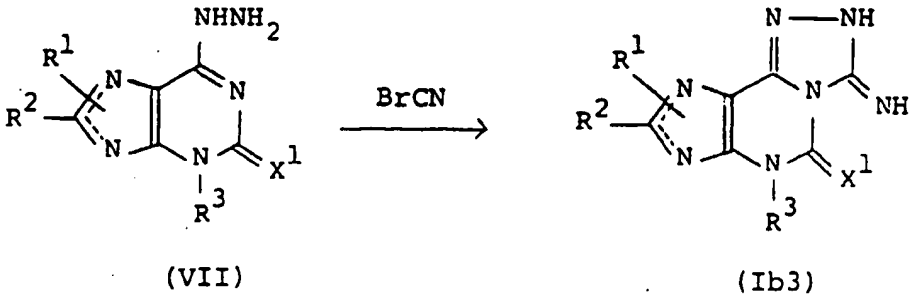
The reaction is performed at 50 to 200°C and completed in 10 minutes to 5 hours.

The starting Compound (VII) is obtained by the process shown in Process 2.

Process 6

Compound (Ib3), which is Compound (I) wherein Y-Z is

is synthesized by the following step.



(VII) (Ib3)

(wherein R^1, R^2, R^3 and X^1 have the same significance as described above.)

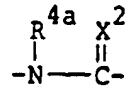
Compound (Ib3) can be synthesized by reacting Compound (VII) with cyanogen bromide.

Any solvent is used so long as it is inert to the reaction. The solvent includes, for example alcohols such as methanol, ethanol, etc.; ethers such as dioxane, tetrahydrofuran, etc., aliphatic nitriles such as acetonitrile, propionitrile, etc.; dimethylalkanamides such as dimethylformamide, dimethylacetamides etc. The solvent is used alone or in combination.

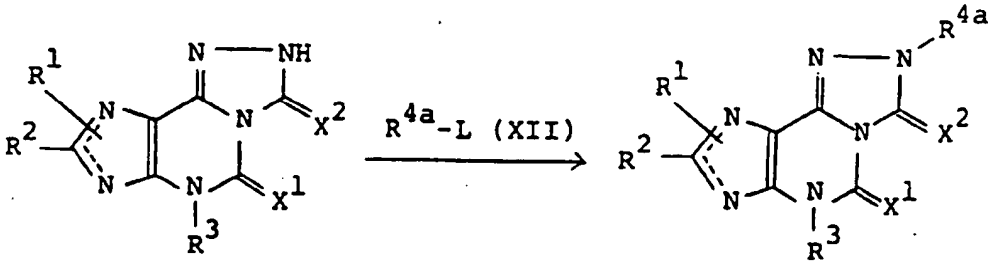
The reaction is performed at 50 to 200°C and completed in 10 minutes to 5 hours.

Process 7

Compound (Ib4) which is Compound (I) wherein Y-Z is



is obtained by the following step.



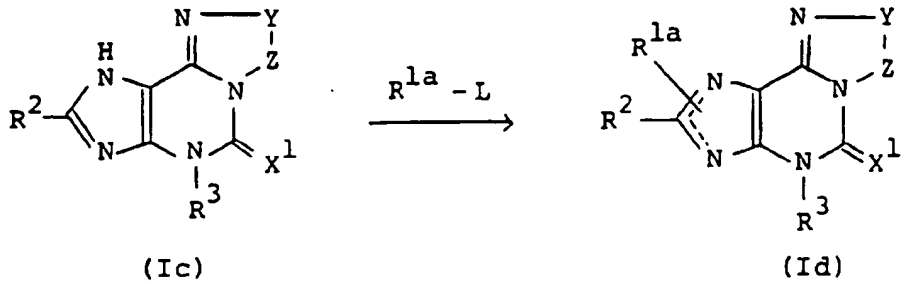
(Ib1), (Ib2), (Ib3) (Ib4)

(wherein R^1, R^2, R^3, X^1 and X^2 have the same significance as described above, and R^{4a} represents a group other than hydrogen in the definition of R^4 described above.)

Compound (Ib4) can be synthesized by reacting Compound (Ib1), (Ib2) or (Ib3) with Compound (XII) in a solvent. The reaction is performed preferably in the presence of a base. Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, ethers such as tetrahydrofuran, dioxane,etc.; dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc; alcohols such as methanol, ethanol, isopropyl alcohol, etc.; or dimethylsulfoxide, etc. The solvent is used alone or in combination. The base includes alkali metal carbonates such as potassium carbonate, sodium carbonate, etc.; hydrated alkali metals such as sodium hydride, potassium hydride, etc.; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, etc. The reaction is performed at 0 to 150°C and completed in 10 minutes to 12 hours.

Process 8

Compound (Id), which is Compound (I) wherein R^{1a} represents a group other than hydrogen in the definition of R^1 is obtained by the following step.



(Ic) (Id)

(wherein R^{1a} represents a group other than hydrogen in the definition of R^1 described above and, X^1, R^2, R^3 and L have the same significance as described above.)

Compound (Id) can be synthesized by reacting Compound (Ic), which is Compound (I) wherein R^1 is hydrogen,

with R^{1a}-L, preferably in the presence of a base.

Any solvent is used so long as it is inert to the reaction. The solvent includes, for example, ethers such as tetrahydrofuran, dioxane,etc., dimethylalkanamides such as dimethylformamide, dimethylacetamide, etc.; alcohols such as methanol, ethanol, isopropyl alcohol, etc.; or dimethylsulfoxide, etc. The solvent is used alone or in combination. The base includes alkali metal carbonates such as potassium carbonate, sodium carbonate, etc.; hydrated alkali metals such as sodium hydride, potassium hydride, etc.; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, etc.

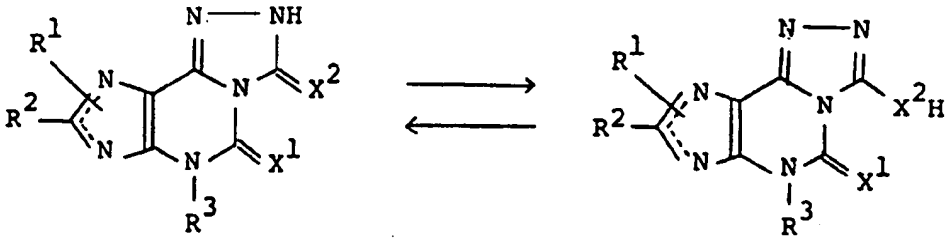
The reaction is performed at 0 to 150°C and completed in 10 minutes to 12 hours.

The intermediates and objective compounds in the respective methods described above is isolated and purified by purification methods conventionally used in organic synthetic chemistry, for example, filtration, extraction, drying, concentration, recrystallization, various column chromatographies, etc. The intermediates can be directly used in the subsequent reaction, without any particular purification.

In the case that it is desired to obtain salts of Compound (I), when Compound (I) is obtained in the form of its salt, Compound (I) is purified as it is. When Compound (I) is obtained in the free form, its salts are formed in a conventional manner, for example, Compound (I) is suspended or dissolved in an appropriate solvent, and an acid or base is added to the solution or suspension.

Furthermore, Compound (I) and pharmaceutically acceptable salts thereof may exist in the form of addition products to water or various solvents; in this case, the pharmaceutically acceptable salts are also included in the present invention.

Furthermore, Compounds (Ib1), (Ib2) and (Ib3) wherein R^4 is hydrogen may be present in the form of Compound (Ibt) as tautomers.

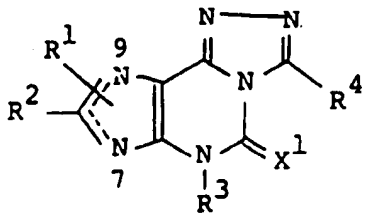


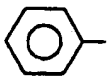
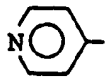
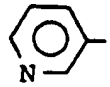
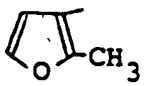
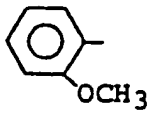
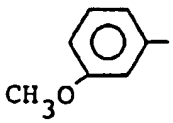
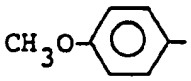
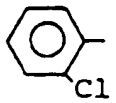
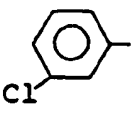
(Ib1), (Ib2), (Ib3) (Ibt)

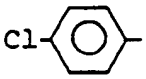
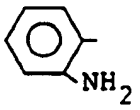
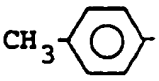
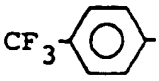
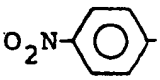
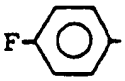
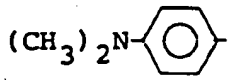
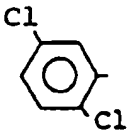
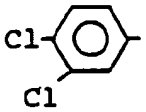
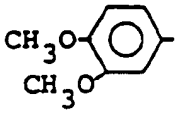
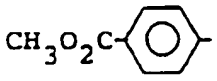
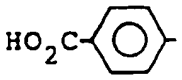
All the possible stereoisomers including the tautomers and mixtures are also included in the scope of the present invention.

Specific examples of Compound (I) obtained by the various methods are shown in Table 1.

Table 1-1



Compound No.	R^1	R^2	R^3	R^4	X^1
1	9-CH_3	H	$(CH_2)_2CH_3$		O
2	9-CH_3	H	$(CH_2)_2CH_3$		O
3	9-CH_3	H	$(CH_2)_2CH_3$		O
4	9-CH_3	H	$(CH_2)_2CH_3$		O
5	9-CH_3	H	$(CH_2)_2CH_3$		O
6	9-CH_3	H	$(CH_2)_2CH_3$		O
7	9-CH_3	H	$(CH_2)_2CH_3$		O
8	9-CH_3	H	$(CH_2)_2CH_3$		O
9	9-CH_3	H	$(CH_2)_2CH_3$		O
10	9-CH_3	H	$(CH_2)_2CH_3$		O
11	9-CH_3	H	$(CH_2)_2CH_3$		O

Compound No.	R^1	R^2	R^3	R^4	X^1
12	9-CH_3	H	$(CH_2)_2CH_3$		O
13	9-CH_3	H	$(CH_2)_2CH_3$		O
14	9-CH_3	H	$(CH_2)_2CH_3$		O
15	9-CH_3	H	$(CH_2)_2CH_3$		O
16	9-CH_3	H	$(CH_2)_2CH_3$		O
17	9-CH_3	H	$(CH_2)_2CH_3$		O
18	9-CH_3	H	$(CH_2)_2CH_3$		O
19	9-CH_3	H	$(CH_2)_2CH_3$		O
20	9-CH_3	H	$(CH_2)_2CH_3$		O
21	9-CH_3	H	$(CH_2)_2CH_3$		O
22	9-CH_3	H	$(CH_2)_2CH_3$		O
23	9-CH_3	H	$(CH_2)_2CH_3$		O
24	9-CH_3	H	$(CH_2)_2CH_3$	CH_3	O
25	H	H	$(CH_2)_2CH_3$	CH_3	O

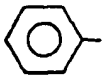
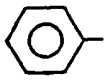
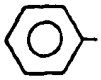
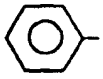
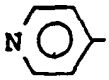
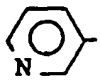
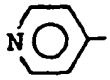
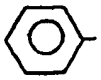
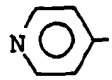
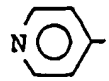
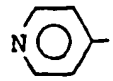
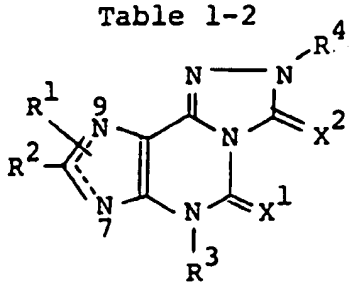
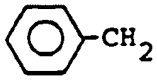
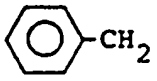
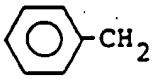
Compound No.	R^1	R^2	R^3	R^4	X^1
26	H		$(CH_2)_2CH_3$		O
27	H		$(CH_2)_2CH_3$	CH_3	O
28	9-CH_3	H	-CH_2- 		O
29	9-CH_3	H			O
30	H	H	$(CH_2)_2CH_3$		O
31	H	H	$(CH_2)_2CH_3$		O
32	H	H	$(CH_2)_2CH_3$		O
33	H	H	$(CH_2)_2CH_3$		O
34	H	H	-CH_2- 		O
35	9-$(CH_2)_2CH_3$	H	$(CH_2)_2CH_3$		O
36	9-CH_3	H	$(CH_2)_2CH_3$	H	O
37	9-CH_3	H	-CH_2- 	CH_3	O
38	H	H	$(CH_2)_3CH_3$		O
39	9-CH_2- 	H	$(CH_2)_2CH_3$		O
40	9-$(CH_2)_2CH_3$	H	$(CH_2)_2CH_3$		O

Table 1-2



Compound No.	R^1	R^2	R^3	X^1	X^2	R^4
41	9-CH_3	H	$CH_3(CH_2)_2$	O	O	H
42	9-CH_3	H		O	O	H
43	H		$CH_3(CH_2)_2$	O	O	H
44	9-$(CH_2)_2CH_3$	H	$CH_3(CH_2)_2$	O	O	H
45	H	H	$CH_3(CH_2)_2$	O	O	H
46	9-CH_3	H	$CH_3(CH_2)_2$	O	S	H
47	9-CH_3	H		O	S	H
48	9-CH_3	H	$CH_3(CH_2)_2$	O	O	C_2H_5
49	9-CH_3	H		O	O	C_2H_5
50	9-CH_3	H	$CH_3(CH_2)_2$	O	NH	H
51	9-CH_3	H	$CH_3(CH_2)_3$	O	O	H

The pharmacological activities of Compound (I) represented by the general formula (I) are illustrated as follows.

(a) Effects on passive Schultz-Dale reaction (broncho-dilatory effects)

Guinea pigs were passively sensitized as follows. Hartley male guinea pigs weighing 350 to 500 g were injected

intraperitoneally with rabbit anti-egg albumin (EWA) serum prepared by the method of Koda et al. [Folia pharmacol., Japon 66, 237, (1970)]. After 24 hours, the guinea pigs were stunned and exsanguinated, and then trachea was excised. The zig-zag strips of the trachea were prepared by the method of Emmerson and Mackay [J. Pharm. Pharmacol., 31, 798, (1979)]. The strips were suspended in Krebs-Henseleit solution at 37°C under aeration of a mixed gas of 95% oxygen and 5% carbon dioxide, and incubated for one hour. Antigen (EWA) was then introduced in the solution (final concentration; 1 µg/ml), and the contraction was measured by isotonictransducer (TD-112s, made by Nihon Kohden K.K., Japan) and recorded on a recorder (Type 3066, made by Yokogawa-Hokushin Denki, K.K. Japan). After the contraction curves reached plateau the compounds were successively added in order to get cumulative concentration-relaxation curves. Concentration of 50% relaxation rate (IC_{50}) was calculated from the regression line, which was obtained from cumulative concentration-relaxation curves.

The results are shown in Table 2.

(b) Effects on experimental asthma

Guinea pigs were passively sensitized as follows. Hartley male guinea pigs weighing 350 to 500 g were intraperitoneally injected with 1 ml of rabbit anti-egg alubmin (EWA) serum prepared by the method of Koda et al. [Folia pharmacol., Japon, 66, 237 (1970)]. The animals were treated with intraperitoneal injection of diphenhydramine (20 mg/kg) and propranolol (5 mg/kg), 30 minutes before administration of test compounds. 17 hours after the sensitization, the test compounds (50 mg/kg or 5 mg/kg) or saline (control) were orally administrated to sensitized animals. After one hour from the administration of the test compounds, the guinea pigs were placed in plastic observation box and were exposed to an aerosal antigen of 1.5% EWA.

The time until the onset of respiratory distress-like symptom [collapse time (second)] was measured as a result of experimental asthma.

The results are shown in Table 2.

(c) Inhibition effect on platelet activating factor (PAF)-induced mortality

The experiment was performed by a minor modification of method of Carlson et al. [Agents and Actions, 21, 379 (1987)]. Groups each consisting of 10 male dd mice (weighing 28 to 32 g) were used, and 100 mg/kg of test compound or a saline (control) was orally administrated. One hour after the administration of test compound, 40 µg/kg of PAF (manufactured by Avanti Polar Lipids Co., Ltd.) was intravenously administered. Two hours after PAF injection, the mortality rate of the animals was observed. The compound whose mortality rate was significantly ($p < 0.05$: Fischer's accurate probability tests) lower than control is regarded as having inhibitory effect on PAF-induced mortality, and the results in Table 2 were represented by minimum effective dose (MED).

Table 2

Compound	Passive Schultz-Dale reaction IC_{50} (µM)	Experimental asthma Collapse time (sec) n=3-10 mean±S.E.M.	PAF-induced mortality MED (mg/kg)
1	4.1		
2	0.40		
3	0.032	422 ± 130	
4	7.7	358 ± 65	
5	0.70		100
6			100
8	5.6		
9	7.8		
10	18		
11	>40		100
12	26	399 ± 55**	100
14	45		
24			100
25	0.42	590 ± 9.8	100
30	0.76		10

** Administration dose of Compound 12 was 5 mg/kg (Administration dose of the other compounds were 50 mg/kg)

Table 2 (continued)

Compound	Passive Schultz-Dale reaction IC_{50} (μM)	Experimental asthma Collapse time (sec) n=3-10 mean±S.E.M.	PAF-induced mortality MED (mg/kg)
31	11	512 ± 52	25
38	>40	401 ± 78	25
44	39.6		
Theophylline*	23	414 ± 47	100
Control		254 ± 18	

* The Merck Index 11th 9212 (1989)

(d) Diuretic activity

Wistar male rats weighing 150 to 300 g were used after fasting for 18 hours. A test compound or saline (control) was orally administered to rats (dose: 25 mg/kg) and urine was taken for 6 hours. The test was performed using 3 groups per test compound, and each group consists of 3 animals. The urine was metered by a measuring cylinder and electrolytes (Na^+ and K^+) in the urine were analyzed by flame photometer (model 775A: Hitachi Ltd.).

The results are shown in Table 3.

Parameters in Table 3 are represented by relative value for control.

Table 3

Compound	Urine volume (%)	Excretion of Na^+ (%)	Excretion of K^+ (%)	Na^+/K^+
Control	100	100	100	1.00
1	255	226	87	3.18
3	274	224	196	1.09
4	177	167	134	1.25
6	223	240	146	1.64
7	173	162	122	1.33
8	170	175	122	1.44
9	253	219	139	1.57
10	162	134	109	1.24
11	255	302	134	2.26
12	198	183	129	1.42
16	170	194	175	1.11
17	178	179	134	1.42
18	155	141	129	1.09
24	160	148	168	1.23
25	161	193	119	1.63

Compound	Urine volume (%)	Excretion of Na^+ (%)	Excretion of K^+ (%)	Na^+/K^+
29	170	155	110	1.41
30	204	220	124	1.77
31	191	196	118	1.66
38	353	293	180	1.63
32	195	196	129	1.52
39	185	184	145	1.27
40Sa*	155	132	136	0.97
44	191	142	128	1.11
49	300	279	173	1.61
51	200	152	152	1.00
Furosemide**	175	164	157	1.05

* 40Sa is hydrochloride salt of Compound 40.

** The Merck Index 11th 4221 (1989).

(e) Effect on renal protecting activity (glycerol-induced renal deficient model):

Renal insufficiency is the condition that homeostasis of body fluid failed to maintain by disorder of renal function. It is well known that subcutaneous or intramuscular administration of glycerol to rat induce acute renal insufficiency characterized by renal tubular disturbance [Can J. Physiol. Pharmacol., 65, 42 (1987)].

Wistar male rats (fasted both food and water for 18 hours) were used. A test compound or saline (control) was intraperitoneally administered (dose: 0.1 ml/100 g) to rats. After 30 minutes rats were anesthesized with ether and the back skin was picked up and 0.8 ml /100 g of 50% glycerol was subcutaneously administered. 24 hours after the glycerol injection, the rats were anesthesized with ether and 5 ml of the blood was collected from the descending aorta. To obtain the serum, after allowing it to stand for 30 minutes or longer, the blood sample was centrifuged at 3000 rpm for 10 minutes. Creatinine in the serum sample was determined using autoanalyzer (AU510, Olympus) cr clinical analysis kit of creatinine (Creatinine Test Wako; by Wako Pure Chemical Ind., Japan). Urea nitrogen in the serum was determined using autoanalyzer (AU510; made by Olympus Optical Co., Ltd, Japan) or clinical analysis kit of urea nitrogen (Urea nitrogen test wako; by Wako Pure Chemical Ind., Japan).

The results are shown in Table 4.

Further, the left kidneys of test compound-treated groups and control groups were taken out from the animals and the kidneys were prepared for pathological sample.

As the result of pathological autopsy for kidneys, it was indicated that the renal insufficiency was improved by the test compounds as shown in Table 4.

Table 4

Compound No.	Creatinine in serum (mg/dl)		Urea nitrogen in serum (mg/dl)	
	Glycerol treated		Glycerol treated	
	Control	Test compound administrated (Significance for control*)	Control	Test compound administrated (Significance for control*)
3	2.64±0.27	1.90±0.15 (p<0.05)		
4	2.64±0.27	1.80±0.11 (p<0.05)		
6	4.76±0.18	2.76±0.27 (p<0.001)	171.1±7.7	100.8±9.3 (p<0.001)
7	4.06±0.30	2.96±0.30 (p<0.05)	143.4±8.1	119.9±11.3 (p<0.05)
8	4.09±0.29	1.97±0.23 (p<0.001)	137.9±7.2	76.4±9.6 (p<0.001)
10	5.01±0.19	2.81±0.33 (p<0.001)		
11	4.09±0.29	2.22±0.16 (p<0.001)	137.9+7.2	91.1±7.8 (p<0.001)
14	4.09±0.29	2.91±0.41 (p<0.05)	137.9±7.2	115.9±16.5 N.S.
19	4.06+0.30	2.73±0.38 (p<0.05)	143.4±8.1	99.1±12.7 (p<0.01)
20	3.17±0.28	1.89±0.33 (p<0.001)	131.9±9.0	70.9±17.1 (p<0.01)
28	5.01±0.19	2.68±0.35 (P<0.001)		
31	5.01±0.19	3.05±0.31 (P<0.001)		
42	3.17±0.28	2.19±0.14 (p<0.01)	131.9±9.0	81.4±9.6 (p<0.01)
44	3.17±0.28	2.10±0.20 (p<0.01)	131.9±9.0	75.9±17.2 (p<0.01)
Aminophylline**	2.03±0.18	1.72±0.07 N.S.	46.2±6.5	30.6±2.0 (P<0.05)
Furosemide***	3.22±0.35	4.17±0.41 N.S.	110.7±9.4	150.3±13.7 (p<0.05)
Normal control	Glycerol untreated 0.50 ± 0.02		Glycerol untreated 15.2 ± 0.9	

* Student-t test was used for level of significance

** The Merck Index 11th 477 (1989)

*** The Merck Index 11th 4221 (1989)

N.S. No significant difference

(f) Effect on electroconvulsive shock (ECS)-induced amnesia:

Male ddy mice (weighing 23 to 29 g) were used and each group consists of 14 to 15 animals. These tests were performed with a step through type passive avoidance apparatus. As experimental apparatus, two rooms (bright and dark) with automatic management system were used. An experimental apparatus is composed of a bright room equipped with 4W of fluorescent light (15 x 9 x 11 cm) and a dark room (15 x 14 x 18 cm), the two rooms are separated by a guillotine door of 3 x 3 cm. The floor of both rooms is stainless steal grid floor and the weak electric current can be send the grid floor of dark room. In the automatic management system, latency of acquisition trial and test trial are measured automatically by controlling with a controller (TK-402, by UNICOM, Japan).

The test compound was dissolved in saline and saline was used as a control. The test compound and the saline (control) were orally administered 60 minutes before the acquisition trial, respectively.

Acquisition trial for learning was performed as follows. An animal placed in the bright room could enter, through the door into the dark room that had a grid on the floor. As soon as the mouse entered the dark room, a scrambled foot-shock (0.18 mA) was delivered to the floor grid for 2 seconds. In the test trial, given 24 hours after the acquisition trial, the animal was again placed in the bright room and the response latency to enter the dark room was measured. The mice which required over 60 seconds to move from the bright room into the dark room were excluded from the test trial. Immediately after the acquisition trial, electric convulsive shock (ECS) (25 mA, 0.2 second, 2000 V) was loaded on mice. The test trial was performed 24 hours after the ECS treatment as follows. The mice received the acquisition trial were placed in the bright room and, latency from the door opening to the entrance of the whole body of animal into the dark room was measured. The maximum measurement time was 600 seconds and latency exceeding 600 seconds was recorded as 600 seconds.

The results are shown in Table 5.

Statistical significance between the control group and test compound treated group was judged by Man Whitney U-test.

Table 5

Test Compound	Dose of test compound (mg/kg)	ECS treatment	Number of animals	Latency of test trial	
				(Sec) mean ± S. E.M.	Comparison of test compound with control
Normal	0	-	15	529.3±26.1	
Control	0	+	30	70.9±13.5	p<0.001*
Compound 41	0.625	+	15	105.9±44.0	No significance
	2.5	+	15	111.3±20.1	p<0.05
	10	+	15	97.4±38.7	No significance
	40	+	15	171.8±43.1	p<0.01

* Comparison of control with normal

(g) Effect on scopolamine-induced amnesia:

Acquisition trial was performed in a manner similar to Experiment (f). Amnestic treatment was performed by intraperitoneal administration of scopolamine (0.5 mg/kg), 30 minutes prior to the acquisition trial. The test trial was performed 24 hours after the acquisition trial and its latency was determined as in Experiment (f).

Preparation of administrated test compound was performed in a manner similar to Experiment (f). Test compound and the saline were orally administered 60 minutes before the acquisition trial, respectively.

The results are shown in Table 6.

Table 6

Test Compound	Dose of test compound (mg/kg)	Scopolamine treatment	Number of animals	Latency of test trial	
				(Sec) mean ± S. E.M.	Comparison of test compound with control
Normal	0	-	30	582.6±11.1	
Control	0	+	30	40.9±8.1	p<0.001*
Compound 41	0.625	+	30	96.8±21.5	p<0.01
	2.5	+	30	115.8±26.6	p<0.01
	10	+	30	53.4±8.9	p<0.05
	40	+	30	74.3±18.8	No significance
Control	0	+	45	37.0±6.2	p<0.001*
Compound 51	0.625	+	15	37.0±11.2	No significance
	2.5	+	15	69.5±16.6	p<0.01
	10	+	15	139.9±45.1	p<0.001
	40	+	15	166.3±49.9	p<0.0001

* Comparison of control with normal

(h) Acute toxicity

The compounds were orally administrated to male dd-mice weighing 20 ± 1 g. Minimum lethal dose (MLD) was determined by observing the mortality for seven days after the administration.

The results are shown in Table 7.

Table 7

Compound No.	MLD (mg/kg)	Compound No.	MLD (mg/kg)	Compound No.	MLD (mg/kg)
1	100	22	>300	41	>300
2	300	23	>300	42	>300
3	100	24	300	43	>300
4	200	25	100	44	>300
5	>300	26	>300	46	>300
6	200	27	>300	48	>300
7	300	28	>300	51	>300
8	>300	29	>300		
9	>300	30	300		
10	300	31	>300		
11	>300	33	>300		
12	>300	36	300		
13	>300	37	>300		
14	>300	38	>300		
15	>300	39	>300		
16	>300	40Sa*	100		
17	>300				
18	>300				
19	>300				
20	>300				
21	>300				

* 40Sa is hydrochloride of Compound 40.

Compounds (I) or their pharmaceutically acceptable salts are used directly or in various dosage forms. In the present invention, pharmaceutical compositions are prepared by homogeneously mixing an effective amount of Compound (I) or its pharmaceutically acceptable salt with pharmaceutically acceptable carrier. It is desirable that the pharmaceutical compositions are an appropriative dosable unit for oral administration or injection administration.

In the preparation of orally administrated forms, any of useful pharmaceutically acceptable carriers are used. In the case of orally administrated liquid preparates such as suspensions and syrups, for example, water, saccharides such as sucrose, sorbitol, fructose, etc., glycols such as polyethyleneglycol, propyleneglycol, etc., oils such as sesame oil, olive oil, soybean oil, etc., antiseptics such as p-hydroxybenzoic acid esters, etc., and flavors such as strawberry flavor, peppermint etc. are used. In the case of powder, pills, capsules and tablets; vehicles such as lactose, glucose, sucrose, mannitol, etc.; disintegrators such as starch, sodium alginate, etc.; lubricants such as magnesium stearate, talc, etc.; binders such as polyvinyl alcohol, hydroxypropyl cellulose, gelatin, etc., surfactants such as fatty acid esters etc., and plasticizers such as glycerine, etc., are used. Tablets and capsules are most useful dosage form for oral administration because of easy administration. In the preparation of tablets and capsules, solid medicament carriers are used.

Injection solutions are prepared with such a carrier as distilled water, a salt solution, a glucose solution, or a mixture of a salt solution and a glucose solution.

Effective dose and the number of administration of Compound (I) or its pharmaceutically acceptable salt depend on modes of administration and ages, body weight, and symptoms, etc. of patients. It is preferable to usually administer 1 to 50 mg/kg of Compound (I) or its pharmaceutically acceptable salt daily in 2 to 3 portions.

Furthermore, Compound (I) is administrated by inhalation in the form of aerosol, finely pulverized powders, or spray solution. In the case of aerosol administration, the present compound is dissolved in a pharmaceutically acceptable solvent, for example, ethyl alcohol or a combination of miscible solvents and then mixed with a pharmaceutically acceptable propellant. The aerosol composition is used by filling it in a pressure-withstanding container composition. It is preferable that the aerosol valve is a metering valve for discharging an effective dosage of aerosol composition as determined in advance.

The present invention will be described in detail below, referring to Examples and Reference Examples.

Hereafter the present invention is described by referring to the examples and the reference examples.

Example 1

6,9-Dihydro-9-methyl-3-phenyl-6-n-propyl-5H-1,2,4-triazolo-[3,4-i]purin-5-one (Compound 1):

After 3.00 g (12.6 mmol) of Compound a prepared in Reference Example 1 was suspended in 75 ml of toluene, 1.72 g (12.6 mmol) of benzoylhydrazine was added to the suspension. The mixture was refluxed for 65 hours under heating. After cooling, 200 ml of chloroform and 100 ml of a 50% saturated aqueous sodium bicarbonate aqueous solution were added, and extracted twice with 50 ml of chloroform. The extracts were combined, then the mixture was washed with a saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated. The residue was recrystallized from ethanol to afford 2.48 g (yield, 60%) of 6-(N'-benzoylhydrazino)-3,7-dihydro-7-methyl-3-n-propyl-2H-purin-2-one (Compound ma) as white needles.

Melting point: 228.9-231.1°C

Elemental analysis: as $C_{16}H_{18}N_6O_2$			
Found (%) :	C 59.05	H 5.68	N 25.84
Calcd. (%):	C 58.88	H 5.56	N 25.75

IR (KBr) vmax (cm^{-1}): 1691, 1655, 1627, 1575

^{1}H-NMR (DMSO-d_6) δ (ppm) : 10.63(s, 1H), 10.41(s, 1H), 7.92-7.84(m, 2H), 7.81(s, 1H), 7.55-7.46(m, 3H), 3.93 (s, 3H), 3.81(t, 2H), 1.75-1.55(m, 2H), 0.88 (t, 3H)

After 160 ml of toluene and 308 mg (1.62 mmol) of p-toluenesulfonic acid were added to 2.64 g (8.10 mmol) of the Compound ma, the mixture was refluxed for 2 hours under heating. Then 150 ml of a saturated aqueous sodium bicarbonate solution was added to the mixture. After insoluble matters were filtered off, the filtrate was extracted twice with 50 ml of chloroform and the combined extracts were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. Recrystallization from ethanol-water gave 1.68 g (yield, 67%) of Compound 1 as white needles.

Melting point: 144.6-146.1°C (ethanol-water)

Elemental analysis: as $C_{16}H_{16}N_6O \cdot 0.2H_2O$			
Found (%):	C 61.37	H 5.11	N 27.01
Calcd. (%):	C 61.37	H 5.11	N 26.94

IR (KBr) vmax (cm^{-1}): 3430(br), 1725, 1650, 1450

^{1}H-NMR ($CDCl_3$) δ (ppm) : 7.75-7.65(m, 2H) , 7.61(s, 1H), 7.55-7.40(m, 3H), 4.20(s, 3H), 4.25-4.15(m, 2H), 1.95-1.75(m, 2H), 0.99(t, 3H)

^{13}C-NMR ($CDCl_3$) δ (ppm): 151.3, 144.7, 143.3, 143.1, 139.6, 130.6, 130.1, 127.7, 127.2, 104.1, 45.5, 34.2, 21.3, 11.1

Example 2

6,9-Dihydro-9-methyl-6-n-propyl-3-(2-thienyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 2):

After 4.00 g (16.8 mmol) of Compound a prepared in Reference Example 1 was suspended in 15 ml of dimethylsulfoxide, 2.87 g (20.2 mmol) of thiophene-2-carboxylic hydrazide was added to the suspension. The mixture was stirred at 160°C for 30 minutes. After cooling, 400 ml of water and 150 ml of chloroform were added to the reaction mixture. The precipitates were collected by filtration to give 4.53 g of a light yellow powder. The NMR studies identified the powder as a mixture (approximately 9 :1) of 3,7-dihydro-7-methyl-3-n-propyl-6-[N'-(2-thienoyl)hydrazino]-2H-purin-2-one (Compound mb) and Compound 2. To 2.30 g of the mixture were added 20 ml of toluene, 20 ml of 1,1,2,2-tetrachloroethane and 659 mg (3.46 mmol) of p-toluenesulfonic acid monohydrate, then the solution was refluxed for 4 hours under heating. After cooling, the solution was concentrated, then 50 ml of chloroform and 50 ml of a saturated aqueous sodium bicarbonate were added. The aqueous layer was extracted twice with 50 ml of chloroform, and the extracts were combined and washed with saturated aqueous sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile gave 1.57 g (yield, 58%) of Compound 2 as a light yellow powder.

Melting point: 206.2-207.1°C (acetonitrile)

Elemental analysis: as $C_{14}H_{14}N_6OS$			
Found (%) :	C 52.94	H 4.56	N 26.40
Calcd. (%) :	C 52.88	H 4.56	N 26.43

IR (KBr) vmax (cm^{-1}) : 1718, 1658

^{1}H-NMR (DMSO-d_6) δ (ppm) : 8.07(s, 1H), 7.92(dd, 1H, J=3.7, 2.0Hz), 7.76(dd, 1H, J=5.1, 2.0Hz), 7.20 (dd, 1H, J=5.1, 3.7Hz), 4.08(t, 2H), 4.06(s, 3H), 1.90-1.70(m, 2H), 0.92(t, 3H)

The substantially same operations as in Example 2 were performed in Examples 3 to 22 except that acylhydrazide shown in Table 8 was used in an equimolar amount instead of thiophene-2-carboxylic hydrazide.

The physicochemical data of Compounds 3 to 22 were given in Table 9.

Example 3

6,9-Dihydro-9-methyl-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 3)

Example 4

6,9-Dihydro-9-methyl-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 4)

Example 5

6,9-Dihydro-3-(2-furyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 5)

Example 6

6,9-Dihydro-9-methyl-3-(2-methyl-3-furyl)-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 6)

Example 7

6,9-Dihydro-3-(2-methoxyphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 7)

Example 8

6,9-Dihydro-3-(3-methoxyphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 8)

Example 9

6,9-Dihydro-3-(4-methoxyphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 9)

Example 10

3-(2-Chlorophenyl)-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 10)

Example 11

3-(3-Chlorophenyl)-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 11)

Example 12

3-(4-Chlorophenyl)-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 12)

Example 13

3-(2-Aminophenyl)-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 13)

Example 14

6,9-Dihydro-9-methyl-3-(4-methylphenyl)-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 14)

Example 15

6,9-Dihydro-9-methyl-6-n-propyl-3-(4-trifluoromethylphenyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 15)

Example 16

6,9-Dihydro-9-methyl-3-(4-nitrophenyl)-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 16)

Example 17

6,9-Dihydro-3-(4-fluorophenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 17)

Example 18

6,9-Dihydro-3-(4-dimethylaminophenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 18)

Example 19

3-(2,5-Dichlorophenyl)-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 19)

Example 20

3-(3,4-Dichlorophenyl)-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 20)

Example 21

6,9-Dihydro-3-(3,4-dimethoxyphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 21)

Example 22

6,9-Dihydro-3-(4-methoxycarbonylphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 22)

Table 8

Example No.	Acyl hydrazide	Yield (%)
3	Isonicotinic hydrazide	43
4	Nicotinic hydrazide	15
5	2-Furoic hydrazide	59
6	3-Methyl-2-furoic hydrazide	69
7	2-Methoxybenzoic hydrazide	60
8	3-Methoxybenzoic hydrazide	43
9	4-Methoxybenzoic hydrazide	63
10	2-Chlorobenzoic hydrazide	58
11	3-Chlorobenzoic hydrazide	33
12	4-Chlorobenzoic hydrazide	49
13	2-Aminobenzoic hydrazide	60
14	4-Methylbenzoic hydrazide	39
15	4-Trifluoromethylbenzoic hydrazide	80
16	4-Nitrobenzoic hydrazide	39
17	4-Fluorobenzoic hydrazide	62
18	4-(N,N-Dimethylamino)benzoic hydrazide	64
19	2,5-Dichlorobenzoic hydrazide	96
20	3,4-Dichlorobenzoic hydrazide	75
21	3,4-Dimethoxybenzoic hydrazide	69
22	4-Carbomethoxybenzoic hydrazide	76

Table 9

Compound No.	Properties	Melting point (°C) (Recrystallization solvent)	Elemental analysis (%) (upper: found lower: calcd.)	I R (KBr) cm^{-1}	M S (m/e) Relative intensity	^{1}H-NMR (Measuring solvent) δ (ppm)
3	light yellow powder	236.8 - 238.4 (Ethanol·Acetonitril)	$C_{15}H_{15}N_7O \cdot 0.8C_2H_3N$ C H N 58.20 4.91 32.15 58.27 5.13 31.93	1718, 1650	-	(DMSO-d_6) 8.72(d,2H,J=4.8Hz), 8.12(s,1H), 7.72(d,2H,J=4.8Hz), 4.10(s,3H), 4.07(t,2H), 1.90-1.70(m,2H), 0.90(t,3H)
4	white needles	170.2 - 171.8 (Acetonitril-Ether)	$C_{15}H_{15}N_7O \cdot 0.8C_2H_3N$ C H N 58.29 4.88 32.18 58.27 5.13 31.93	1715, 1650	-	(DMSO-d_6) 8.87(brs,1H), 8.70(brs,1H), 8.14(s,1H), 8.11(s,1H), 7.55(dd,1H), 4.10(s,3H), 4.06(t,2H), 1.85-1.65(m,2H), 0.90(t,3H)
5	white needles	243.5 - 248.5 (Ethanol)	$C_{14}H_{14}N_6O_2$ C H N 56.51 4.93 27.95 56.37 4.73 28.17	1712, 1651	-	($CDCl_3$) 7.67(dd,1H), 7.61(s,1H), 7.39(dd,1H), 6.59(dd,1H), 4.22(t,2H), 4.19(s,3H), 2.00-1.80(m,2H), 1.02(t,3H)
6	white needles	178.7 - 179.1 (Isopropanol)	$C_{15}H_{16}N_6O_2$ C H N 57.36 5.03 26.93 57.68 5.16 26.91	1709, 1656	-	($CDCl_3$) 7.60(s,1H), 7.39(d,1H,J=2.0Hz), 6.71(d,1H,J=2.0Hz), 4.20(t,2H), 4.19(s,3H), 2.52(s,3H), 1.93-1.75(m,2H), 1.00(t,3H)

Compound No.	Properties	Melting point (°C) (Recrystallization solvent)	Elemental analysis (%) (upper: found lower: calcd.)	I R (KBr) cm^{-1}	M S (m/e) Relative intensity	^{1}H-NMR (Measuring solvent) δ (ppm)
7	light yellow powder	164.4 - 165.1 (Isopropanol)	$C_{17}H_{18}N_6O_2$ C H N 60.18 5.21 24.82 60.34 5.36 24.84	1716, 1650, 1473, 1450	-	($CDCl_3$) 7.59(s,1H), 7.53-7.47(m,2H), 7.10-6.97(m,2H), 4.19(s,3H), 4.15(t,3H), 3.76(s,3H), 1.93-1.77(m,2H), 0.99(t,3H)
8	white needles	165.4 - 166.8 (Toluene)	$C_{17}H_{18}N_6O_2$ C H N 60.18 5.40 24.54 60.34 5.36 24.84	1722, 1649, 1570, 1449	-	($CDCl_3$) 7.61(s,1H), 7.43-7.26(m,3H), 7.08-7.03(m,1H), 4.20(s,3H), 4.22-4.16(m,2H), 3.86(s,3H), 1.95-1.75(m,2H), 0.98(t,3H)
9	white needles	161.0 - 163.3 (Toluene-Cyclohexane)	$C_{17}H_{18}N_6O_2$ C H N 60.55 5.49 25.24 60.34 5.36 24.84	3105, 2960, 1715, 1650, 1483	-	(DMSO-d_6) 8.07(s,1H), 7.64(d,2H,J=6.8Hz), 7.03(d,2H,J=6.8Hz), 4.08(s,3H), 4.04(t,2H), 3.84(s,3H), 1.80-1.60(m,2H), 0.89(t,3H)
10	white needles	163.4 - 165.2 (Toluene-Cyclohexane)	$C_{16}H_{15}N_6OCl$ C H N 56.19 4.28 24.42 56.06 4.41 24.52	1721, 1649, 1567, 1449, 1436	-	(DMSO-d_6) 8.12(s,1H), 7.65-7.45(m,4H), 4.10(s,3H), 4.03(t,2H), 1.80-1.60(s,2H), 0.87(t,3H)

Compound No.	Properties	Melting point (°C) (Recrystallization solvent)	Elemental analysis (%) (upper: found lower: calcd.)	I R (KBr) cm^{-1}	M S (m/e) Relative intensity	^{1}H-NMR (Measuring solvent) δ (ppm)
11	white needles	142.9 - 143.8 (Ethanol)	$C_{16}H_{16}N_6OCl$ C H N 56.40 4.23 24.63 56.06 4.41 24.52	1708, 1659, 1447, 1299	-	($CDCl_3$) 7.78-7.77(m,1H), 7.66-7.62(m,1H), 7.62(s, 1H), 7.51-7.39(m,2H), 4.21(s,3H), 4.20(t,2H), 1.95-1.75(m,2H), 0.99 (t,3H)
12	white needles	175.1 - 177.0 (Toluene-Cyclohexane)	$C_{16}H_{15}N_6OCl$ C H N 55.79 4.45 24.70 56.06 4.41 24.52	1728, 1657, 1470, 1450	-	(DMSO-d_6) 8.09(s,1H), 7.73(d,2H,J=7.5Hz), 7.56 (d,2H,J=7.5Hz), 4.09(s, 3H), 4.05(t,2H), 1.85-1.65(m,2H), 0.89(t,3H)
13	light yellow powder	177.1 - 177.8 (Ethanol-water)	$C_{16}H_{17}N_7O$ C H N 59.10 5.47 30.67 59.43 5.30 30.32	3420, 3350, 1710, 1655, 1448	-	(DMSO-d_6) 8.06(s,1H), 7.20-7.05(m,2H), 6.70 (d,1H), 6.57(t,1H), 5.20(brs,2H), 4.09(s, 3H), 4.00(t,2H), 1.80-1.60(m,2H), 0.88(t,3H)
14	white needles	169.9 - 171.2	$C_{17}H_{18}N_6O$ C H N 63.62 5.53 26.39 63.34 5.63 26.07	1708, 1646, 1478, 1445	-	($CDCl_3$) 7.64(d,2H,J= 8.0Hz), 7.60(s,1H), 7.29(d,2H,J=8.0Hz), 4.20(s,3H), 4.19(t,2H), 2.43(s,3H), 1.93-1.77 (m,2H), 0.98(t,3H)

Compound No.	Properties	Melting point (°C) (Recrystallization solvent)	Elemental analysis (%) (upper: found lower: calcd.)	I R (KBr) cm^{-1}	M S (m/e) Relative intensity	^{1}H-NMR (Measuring solvent) δ (ppm)
15	white needles	205.8 - 207.0 (Isopropanol)	$C_{17}H_{15}N_6F_3O$ C H N 54.0 3.78 22.13 54.25 4.02 22.33	1707, 1652, 1574, 1450, 1409	-	($CDCl_3$) 7.91(d,2H,J=8.0 Hz), 7.75(d,2H,J=8.0Hz), 7.64(s,1H), 4.22(s,3H), 4.20(t,2H), 1.97-1.77(m, 2H), 1.00(t,3H)
16	white needles	117.0 - 117.2 (Toluene)	$C_{16}H_{15}N_7O_3 \cdot 0.3H_2O$ C H N 53.56 4.27 27.46 53.57 4.38 27.33	1707, 1655, 1515, 1449	-	($CDCl_3$) 8.35(d,2H,J=9.0 Hz), 7.98(d,2H,J=9.0Hz), 7.66(s,1H), 4.22(s,3H), 4.21(t,2H), 1.95-1.77 (m,2H), 1.00(t,3H)
17	light yellow needles	192.0 - 193.9 (Ethanol-water)	——	3400, 1722, 1657, 1482, 1451	326(M^+, 100) 297(12) 284(33) 283(42) 163(12)	($CDCl_3$) 7.77(dd,1H,J= 6.3,8.7Hz), 7.61(s,1H), 7.18(dd,1H,J=8.7,8.7Hz), 4.22(t,2H), 4.20(s,3H), 1.93-1.75(m,2H), 0.99 (t,3H)
18	white needles	255.9 - 256.2 (Isopropanol)	$C_{18}H_{21}N_7O \cdot 1/5HCl$ C H N 60.36 5.89 27.36 60.27 5.96 27.33	1706, 1651, 1612, 1478, 1449	-	($CDCl_3$) 7.73(d,2H,J=9.0 Hz), 7.59-7.04(brd,2H), 4.20(s,3H), 4.19(t,2H), 3.08(s,6H), 2.00-1.75 (m,2H), 0.99(t,3H)

Compound No.	Properties	Melting point (°C) (Recrystallization solvent)	Elemental analysis (%) (upper: found lower: calcd.)	I R (KBr) cm^{-1}	M S (m/e) Relative intensity	^1H-NMR (Measuring solvent) δ (ppm)
19	white needles	257.3 - 258.1 (Acetonitril)	$C_{16}H_{14}N_6Cl_2O$ C H N 50.98 3.54 22.15 50.94 3.74 22.28	1722, 1650, 1571, 1448	-	($CDCl_3$) 7.63(s,1H), 7.56(m,1H), 7.45-7.43 (m,2H), 4.21(s,3H), 4.17(t,3H), 1.93-1.75 (m,2H), 0.97(t,3H)
20	white needles	175.0 - 176.1 (Ethanol-water)	$C_{16}H_{14}N_6OCl_2 \cdot 0.6H_2O$ C H N 49.27 3.69 21.39 49.52 3.95 21.66	1720, 1650, 1571, 1450	378(M^++2, 66), 376 (M^+, 100) 336(22), 335(32), 334(35), 333(37)	($CDCl_3$) 7.90-7.89(m,1H), 7.63(s,1H), 7.64-7.54(m, 2H), 4.20(s,3H), 4.19 (t,2H), 1.97-1.78(m,2H), 1.00(t,3H)
21	white powder	211 - 215 (Dioxane)	$C_{18}H_{20}N_6O_3$ C H N 58.46 5.30 23.16 58.67 5.48 22.82	1723, 1652, 1499, 1447	-	($CDCl_3$) 7.60(s,1H), 7.38-7.33(m,2H), 6.98 (d,1H,J=8.2Hz), 4.21(t, 2H), 4.20(s,3H), 3.95 (s,3H), 3.94(s,3H), 1.97-1.78(m,2H), 0.99 (t,3H)
22	white needles	251.3 - 252.9 (Toluene)	$C_{18}H_{18}N_6O_3$ C H N 59.13 5.17 22.82 59.01 4.95 22.94	1715, 1653, 1611, 1568, 1439	-	(DMSO-d_6) 8.11(s,1H), 8.06(d,2H,J=8.5Hz), 7.86(d,2H,J=8.6Hz), 4.10(s,3H), 4.05(t,2H), 3.91(s,3H), 1.82-1.62 (m,2H), 0.89(t,3H)

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Example 23

6,9-Dihydro-3-(4-carboxyphenyl)-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 23):

After 3.00 g (8.20 mmol) of Compound 22 prepared in Example 22 was dissolved in 30 ml of dimethylsulfoxide, 11.7 g (82 mmol) of lithium iodide was added and the mixture was stirred at 140°C for 13 hours. After cooling, 500 ml of water was added to the solution followed by extraction 10 times with 50 ml of chloroform-methanol (10 : 1). The extracts were combined and washed with 0.2 M sodium thiosulfate aqueous solution and with a saturated aqueous sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% methanol/chloroform), and triturated with 10 ml of methanol to afford 1.40 g (yield, 49%) of Compound 23 as a light yellow powder.

Melting point: >315°C

IR (KBr) vmax (cm^{-1}): 3400, 1728, 1700, 1650, 1593, 1553

^{1}H-NMR (DMSO-d_6) δ (ppm): 8.09(s, 1H), 8.05(d, 2H, J=8.3Hz), 7.74(d, 2H, J=8.3Hz), 4.09(s, 3H), 4.04(t, 2H), 1.82-1.62(m, 2H), 0.89(t, 3H)

MS (m/e: relative intensity): 352(M^+, 100), 310(59), 309(79)

Example 24

6,9-Dihydro-3,9-dimethyl-6-n-propyl-5H-1,2,4-triazolo-[3,4-i]purin-5-one (Compound 24):

After 100 ml of toluene and 1.49 g (20.2 mmol) of acetohydrazide were added to 4.00 g (16.8 mmol) of Compound a prepared in Reference Example 1, the mixture was refluxed for 53 hours under heating. After cooling, the solution was concentrated, 100 ml of chloroform and 50 ml of 50% saturated sodium bicarbonate aqueous solution were added and the aqueous layer was extracted twice with 30 ml of chloroform. The extracts were combined and washed with a saturated aqueous sodium chloride. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 2% methanol/chloroform) to afford 1.39 g (yield, 34%) of Compound 24 as a white powder.

Melting point: 191.9-193.6°C (acetonitrileethanol)

Elemental analysis: as $C_{11}H_{14}N_6O.3/4CH_3CN\cdot1/5C_2H_5OH$			
Found (%):	C 54.21	H 5.99	N 32.84
Calcd. (%):	C 54.12	H 6.14	N 33.03

IR (KBr) vmax (cm^{-1}): 1715, 1655, 1450

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.57(s, 1H), 4.19(t, 2H), 4.14(s, 3H), 2.95(s, 3H), 1.95-1.80(m, 2H), 1.02(t, 3H)

^{13}C-NMR ($CDCl_3$) δ (ppm): 149.1, 145.7, 143.1, 142.7, 139.2, 104.2, 45.18, 34.1, 21.3, 13.4, 11.1

Example 25

6,9-Dihydro-3-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]-purin-5-one (Compound 25):

After 5 ml of dimethylsulfoxide and 730 mg (9.82 mmol) of acetohydrazide were added to 2.00 g (8.93 mmol) of Compound b prepared in Reference Example 2, the mixture was stirred at 160°C for 30 minutes. After cooling, the 200 ml of water and 50 ml of chloroform were added to the solution. After fractionation, the aqueous layer was extracted twice with 50 ml of chloroform. The extracts were combined and washed twice with water and once with a saturated aqueous sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 5% methanol/chloroform) to afford 1.16 mg (yield, 52%) of Compound 25 as a white powder.

Melting point: 298.0-299.2°C (ethanol)

Elemental analysis: as $C_{10}H_{12}N_6O\cdot0.1H_2O$			
Found (%):	C 51.58	H 5.25	N 35.62
Calcd. (%):	C 51.32	H 5.25	N 35.90

IR (KBr) vmax (cm^{-1}): 1715, 1662

^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.78(brs, 1H) , 8.01(s, 1H), 4.08(t, 2H), 2.76(s, 3H), 1.95-1.70(m, 2H), 0.92(t, 3H)

Example 26

8-Cyclopentyl-6,9-dihydro-6-n-propyl-3-phenyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 26):

After 2.00 g (6.85 mmol) of Compound c prepared in Reference Example 3 was dissolved in 50 ml of toluene, 1.40 g (10.28 mmol) of benzoylhydrazine was added to the solution. The mixture was refluxed for 4 hours and a half under heating. After cooling, 100 ml of chloroform was added to the reaction solution. The precipitates were collected by filtration to afford 2.22 g (yield, 86%) of 6-(N'-benzoylhydrazino)-8-cyclopentyl-3,7-dihydro-3-n-propyl-2H-purin-2-one (Compound mc) as a white powder.

Melting point: 223.1-224.9°C

Elemental analysis: as $C_{20}H_{24}N_6O_2$			
Found (%):	C 63.10	H 6.30	N 22.01
Calcd. (%):	C 63.14	H 6.36	N 22.09

IR (KBr) νmax (cm^{-1}): 1680, 1614, 1574, 1504

^{1}H-NMR (DMSO-d_6) δ (ppm) : 12.8-12.3(brs, 1H), 10.7-10.2(br, 2H), 8.04-7.89(m, 2H), 7.65-7.48(m, 3H), 3.83 (t, 2H), 3.30-3.10(m, 1H), 2.20-1.60(m, 10H), 0.87(t, 3H)

1.07 g of Compound 26 as white needles was obtained from 1.89 g (4.97 mmol) of the Compound mc by similar manner to Example 1 (yield, 59%).

Melting point: 252.9-254.5°C (ethanol-water)

Elemental analysis: as $C_{20}H_{22}N_6O$			
Found (%):	C 66.54	H 6.20	N 23.25
Calcd. (%):	C 66.28	H 6.12	N 23.19

IR (KBr) νmax (cm^{-1}): 1720, 1660

^{1}H-NMR (DMSO-d_6) δ (ppm): 13.55(brs, 1H), 7.80-7.60(m, 2H), 7.55-7.40(m, 3H), 4.05(t, 2H), 3.35-3.15(m, 1H), 2.15-1.55(m, 10H), 0.89(t, 3H)

Example 27

8-Cyclopentyl-6,9-dihydro-3-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 27):

The procedure was performed in a manner similar to Example 26 except for using 760 mg (10.28 mmol) of acetohydrazide instead of benzoylhydrazine. Thus, 1.92 g (yield, 88%) of 8-cyclopentyl-6-(N'-acetylhydrazino)-3,7-dihydro-3-n-propyl-2H-purin-2-one (Compound md) was obtained as a white powder.

Melting point: >270°C

Elemental analysis: as $C_{15}H_{22}N_6O_2$			
Found (%):	C 56.25	H 6.98	N 26.34
Calcd. (%) :	C 56.59	H 6.97	N 26.40

IR (KBr) νmax (cm^{-1}): 1667, 1651, 1539

1.51 g of Compound 27 as white needles was obtained from 1.84 g (5.79 mmol) of Compound md by a similar manner to Example 1 (yield, 87%).

Melting point: 307.6-309.4°C (isopropanol)

Elemental analysis: as $C_{15}H_{20}N_6O_1$			
Found (%):	C 60.33	H 6.84	N 27.65
Calcd. (%):	C 59.98	H 6.71	N 27.98

IR (KBr) vmax (cm^{-1}): 1720, 1660

^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.39(brs, 1H), 4.04(t, 2H), 3.30-3.10(m, 1H), 2.75(s, 3H), 2.10-1.55(m, 10H), 0.91(t, 3H)

Example 28

6-Benzyl-6,9-dihydro-9-methyl-3-phenyl-5H-1,2,4-triazolo-[3,4-i]purin-5-one (Compound 28):

Using 4.00 g (14.0 mmol) of Compound h in Reference Example 8 and 2.28 g (16.8 mmol) of benzoyl hydrazine, the procedure was carried out in a manner similar to Example 2 to give 2.69 g (yield, 54%) of Compound 28 as light yellow needles.

Melting point: 255.3-256.9°C (toluene)

Elemental analysis: as $C_{20}H_{16}N_6O \cdot H_2O$			
Found (%):	C 67.22	H 4.37	N 23.16
Calcd. (%):	C 67.07	H 4.56	N 23.46

IR (KBr) vmax (cm^{-1}): 1717, 1650, 1567, 1451

^{1}H-NMR (DMSO-d_6) δ (ppm) : 8.09(s, 1H), 7.72-7.67(m, 2H), 7.56-7.44(m, 3H), 7.40-7.35(m, 2H), 7.34-7.20(m, 3H), 5.28(s, 2H), 4.10(s, 3H)

Example 29

6,9-Dihydro-3,6-diphenyl-9-methyl-5H-1,2,4-triazolo[3,4-i]-purin-5-one (Compound 29):

Except that 3.50 g (12.9 mmol) of Compound k in Reference Example 10 and 2.10 g (15.4 mmol) of benzoylhydrazine were used, the procedure was performed in a manner similar to Example 2. Thus, 962 mg (yield, 22%) of Compound 29 was obtained as a white powder

Melting point: 267.9-269.7°C (N,N'-dimethylformamide-water)

Elemental analysis: as $C_{19}H_{14}N_6O$			
Found (%):	C 66.35	H 3.81	N 24.84
Calcd. (%) :	C 66.66	H 4.12	N 24.55

IR (KBr) vmax (cm^{-1}): 1717, 1655, 1429

^{1}H-NMR (DMSO-d_6) δ (ppm) : 7.97(s, 1H), 7.73-7.67(m, 2H), 7.57-7.41(m, 8H), 4.11(s, 3H)

Example 30

6,9-Dihydro-3-phenyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 30):

The procedure was performed in a manner similar to Example 2 except for using 8.27 g (24.0 mmol) of Compound f obtained in Reference Example 6 and 3.93-g (28.8 mmol) of benzoylhydrazide. Thus, 6.90 g (yield, 69%) of 8-benzyloxymethyl-6,9-dihydro-3-phenyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound me) was obtained as a light yellow powder.

^{1}H-NMR (90 MHz; $CDCl_3$) δ (ppm) : 7.75 (s, 1H), 7.80-7.65 (m, 2H), 7.60-7.45(m, 3H), 7.24(brs, 5H), 5.93 (s, 2H), 4.78(s, 2H), 4.18(t, 2H), 2.00-1.60(m, 2H), 0.99(t, 3H)

After 6.71 g (16.2 mmol) of the Compound me was suspended in 325 ml of toluene, 32.4 ml of 1 M boron tribromide in methylene chloride was dropwise added to the suspension under ice cooling. The mixture was stirred at room temperature for 2 hours. The reaction mixture was poured onto ice water followed by extraction 3 times with 100 ml of chloroform. The extracts were combined and washed with a saturated aqueous sodium chloride. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The precipitates were collected by filtration and then washed with methanol. The crystals were recrystallized from isopropanol to give 2.52 g (yield, 53%) of Compound 30 as white needles.

Melting point: 272.8-280.0°C (acetonitrile)

Elemental analysis: as $C_{15}H_{14}N_6O \cdot 0.1H_2O \cdot 0.5C_2H_3N$			
Found (%):	C 60.69	H 4.75	N 28.83
Calcd. (%):	C 60.69	H 5.00	N 28.75

IR (KBr) vmax (cm^{-1}): 1720, 1660

^{1}H-NMR (DMSO-d_6) δ (ppm) : 14.10-13.80(brs, 1H), 8.11 (s, 1H), 7.80-7.70(m, 2H), 7.60-7.45(m, 3H), 4.08 (t, 2H), 1.90-1.70(m, 2H), 0.90(t, 3H)

Example 31

6,9-Dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 31):

The procedure was performed in a manner similar to Example 2 except for using 4.00 g (11.6 mmol) of Compound f prepared in Reference Example 6 and 1.91 g (14.0 mmol) of isonicotinic hydrazide. Thus, 2.32 g (yield, 48%) of 8-benzyloxymethyl-6,9-dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one(Compound mf) obtained as a yellow powder.

^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm) : 8.73(d, 2H, J=8.9Hz), 7.78(s, 1H), 7.69(d, 2H, J=8.9Hz), 7.23(brs, 5H), 5.93 (s, 2H), 4.78(s, 2H), 4.20(t, 2H), 2.00-1.65 (m, 2H), 1.01(t, 3H)

1.09 g of Compound 31 as white needles was obtained from 2.10 g of Compound mf by the similar elimination reaction of the protecting group to Example 30 (yield, 73%).

Melting point: >330°C (DMF-dioxan-water)

Elemental analysis: as $C_{14}H_{13}N_7O \cdot 0.8H_2O$			
Found (%):	C 32.02	H 4.51	N 32.02
Calcd. (%):	C 31.67	H 4.75	N 31.66

IR (KBr) vmax (cm^{-1}): 1732, 1659, 1603, 1568, 1514,

^{1}H-NMR (DMSO-d_6) δ (ppm) : 14.03(s, 1H), 8.71 (d, 2H, J=5.5Hz), 8.14(s, 1H), 7.73(m, 2H), 4.10(t, 2H), 1.85-1.65 (m, 2H), 0.91(t, 3H)

Example 32

6,9-Dihydro-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 32):

The procedure was performed in a manner similar to Example 2 except for using 3.50 g (10.2 mmol) of Compound f prepared in Reference Example 6 and 1.68 g (12.2 mmol) of nicotinic acid hydrazide. Thus, 2.87 g (yield, 53%) of 8-benzyloxymethyl-6,9-dihydro-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound mg) was obtained as a yellow powder.

^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm) : 9.05-8.90(m, 1H), 8.80-8.65(m, 1H), 8.20-7.95(m, 1H), 7.77(s, 1H), 7.55-7.25 (m, 1H), 7.23(brs, 5H), 5.93(s, 2H), 4.78(s, 2H), 4.20(t, 2H), 2.05-1.70(m, 2H), 1.01(t, 3H)

503 mg of Compound 32 as white needles was obtained (yield, 28%) from 2.50 g (6.02 mmol) of Compound mg and 4 equivalents of boron tribromide by the similar elimination reaction of the protecting group to Example 30.

Melting point: 277.2-278.2°C (dioxan)

IR (KBr) vmax (cm^{-1}) : 1721, 1654, 1571

^{1}H-NMR (DMSO-d_6) δ(ppm): 14.15-13.80(br, 1H), 8.90 (brs, 1H), 8.71(brs, 1H), 8.18-8.14(m, 1H), 8.12 (s, 1H), 7.56(dd, 1H, J=5.0, 7.5Hz), 4.10(t, 2H), 1.85-1.65(m, 2H), 0.91(t, 3H)

MS (m/e; relative intensity): 285(M^+, 100), 253(68)

Elemental analysis: as $C_{14}H_{13}N_7O \cdot 0.2H_2O$			
Found (%):	C 56.12	H 4.39	N 32.82
Calcd (%):	C 56.26	H 4.52	N 32.80

Example 33

6,9-Dihydro-6-n-propyl-3-(2-thienyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 33):

The procedure was performed in a manner similar to Example 2 except for using 4.50 g (13.1 mmol) of Compound f obtained in Reference Example 6 and 2.23 g (15.7 mmol) of 2-thiophenecarboxylic acid hydrazide. Thus 2.87 g (yield, 52%) of 8-benzyloxymethyl-6,9-dihydro-6-n-propyl-3-(2-thienyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound mh) was obtained as a light red powder.

^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm): 8.05-7.90(m, 1H), 7.74 (s, 1H), 7.60-7.45(m, 1H), 7.35-7.05(m, 6H), 5.92(s, 2H), 4.77(s, 2H), 4.21(t, 2H), 2.05-1.65 (m, 2H), 1.03(t, 3H)

1.63 g of Compound 33 as white needles was obtained from 2.65 g (6.31 mmol) of Compound mh by the similar elimination reaction of the protecting group to Example 30 (yield, 87%).

Melting point: 286.8-290.9°C (N,N-dimethylformamide-water)

Elemental analysis: as $C_{13}H_{12}N_6OS$			
Found (%):	C 52.18	H 3.74	N 28.02
Calcd. (%):	C 51.99	H 4.03	N 27.98

IR (KBr) vmax (cm^{-1}): 1721, 1660

^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.93(brs, 1H), 8.08(s, 1H), 7.93(dd, 1H, J=1.2, 3.6Hz), 7.76(dd, 1H, J=1.2, 5.2Hz), 7.19(dd, 1H, J=3.6, 5.2Hz), 4.13(t, 2H), 1.90-1.70(m, 2H), 0.93(t, 3H)

Example 34

6-Benzyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 34):

The procedure was carried out in a manner similar to Example 31 except for using 3.50 g (8.90 mmol) of Compound m obtained in Reference Example 11 instead of Compound f. Thus, 1.06 g (yield, 36%) of Compound 34 (free form) was obtained as a light yellow powder. The powder was suspended in 10 ml of methanol and 1 ml of hydrogen chloride-saturated methanol solution was added to the suspension. The precipitates were collected by filtration to afford 560 mg (yield, 45%) of the hydrochloride of Compound 34 as a yellow powder.

Melting point: >290°C

IR (KBr) vmax (cm^{-1}): 1712, 1655, 1631

^{1}H-NMR (90MHz; DMSO-d_6) δ (ppm): 9.10-8.75(br, 2H), 8.20-8.05(m, 2H), 8.14(s, 1H), 7.50-7.10(m, 5H), 5.23 (s, 2H)

MS (m/e; relative intensity): 343(M^+, 76), 91(100)

Example 35

6,9-Dihydro-6,9-di-n-propyl-3-phenyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 35):

After 500 mg (1.70 mmol) of Compound 30 obtained in Example 30 was dissolved in 5 ml of N,N'-dimethylformamide, 81.6 mg (2.04 mmol) of 60% sodium hydride was added to the solution at 0°C. 15 minutes after, 0.25 ml (2.51 mmol) of propyl iodide was added to the reaction solution at 0°C. The solution was stirred at room temperature for 30 minutes. After 20 ml of saturated ammonium chloride was added to the reaction solution at 0°C, the mixture was extracted 3 times with 30 ml of chloroform. The extracts were combined and washed with a saturated sodium chloride aqueous solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent: 2% methanol/chloroform) to afford 434 mg (yield, 76%) of Compound 35 as white needles.

Melting point: 215.1-216.8°C (ethanol)

Elemental analysis: as $C_{18}H_{20}N_6O$			
Found (%):	C 64.10	H 6.08	N 25.08
Calcd. (%):	C 64.27	H 5.99	N 24.98

IR (KBr) vmax (cm^{-1}): 1710, 1651

^{1}H-NMR (DMSO-d_6) δ (ppm): 8.15(s, 1H), 7.73-7.66(m, 2H), 7.53-7.40(m, 3H), 4.39(t, 2H), 4.06(t, 2H), 2.10-1.95 (m, 2H), 1.83-1.66(m, 2H), 0.91(t, 3H), 0.90(t, 3H)

Example 36

6,9-Dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 36):

After 15 ml of ethyl orthoformate was added to 800 mg (3.60 mmol) of Compound n prepared in Reference Example 12, the mixture was refluxed for 2 hours under heating. After the reaction solution was allowed to stand over day and night, the precipitates were collected by filtration to give 760 mg (yield, 91%) of Compound 36 as a light red plate.

Melting point: 217.8-218.2°C

IR (KBr) vmax (cm^{-1}): 1696, 1649

^{1}H-NMR (DMSO-d_6) δ (ppm) : 9.16(s, 1H), 8.02(s, 1H), 4.10(t, 2H), 4.04(s, 3H), 2.00-1.55(m, 2H), 0.92(t, 3H)

MS (m/e: relative intensity): 232(M$^+$, 48), 190(84), 189(100)

Example 37

6-Benzyl-6,9-dihydro-3-methyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 37):

The procedure was performed in a manner similar to Example 25 except for using 2.20 g (8.08 mmol) of Compound j prepared in Reference Example 8. Thus, 1.40 g (yield, 62%) of Compound 37 was obtained as a light yellow powder.

Melting point: 308.9-310.3°C

Elemental analysis: as $C_{14}H_{12}N_6O \cdot 0.2H_2O$			
Found (%):	C 59.17	H 3.99	N 30.01
Calcd. (%) :	C 59.23	H 4.40	N 29.60

IR (KBr) vmax (cm^{-1}): 1720, 1659

^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.83(brs, 1H), 8.03(s, 1H), 7.45-7.20(m, 5H), 5.30(s, 2H), 2.76(s, 3H)

Example 38

6-n-Butyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo-[3,4-i]purin-5-one (Compound 38):

The procedure was performed in a manner similar to Example 2 except for using 5.61 g (15.7 mmol) of Compound r prepared in Reference Example 16 and 2.36 g (17.2 mmol) of isonicotinic hydrazide. Thus, 4.42 g of (yield, 66%) of 8-benzyloxymethyl-6-n-butyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound mi) was obtained as a yellow powder.

^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm): 8.71(d, 2H, J=8.8Hz), 7.78(s, 1H), 7.68(d, 2H, J=8.8Hz), 7.22(brs, 5H), 5.93 (s, 2H) , 4.77(s, 2H), 4.22(t, 2H) , 2.00-1.25 (m, 4H), 0.98(t, 3H).

2.82 g of Compound 38 as white needles was obtained (yield, 89%) from 4.42 g of Compound mi by the similar elimination reaction of the protecting group in Example 30.

Melting point: 271.0-272.3°C (isopropanol)

Elemental analysis: as $C_{15}H_{15}N_7O$			
Found (%):	C 58.13	H 4.97	N 31.49
Calcd. (%):	C 58.24	H 4.89	N 31.70

IR (KBr) vmax (cm^{-1}): 1718, 1654

^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.95(brs, 1H), 8.70(d, 2H, J=5.6Hz), 8.12(s, 1H), 7.72(d, 2H, J=5.6Hz), 4.11(t, 2H), 1.80-1.65(m, 2H), 1.45-1.30(m, 2H), 0.89(t, 3H)

Example 39

9-Benzyl-6,9-dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 39):

Except that 7.00 g (17.9 mmol) of Compound s obtained in Reference Example 17 and 2.71 g (19.7 mmol) of isonicotinic hydrazide were used, the procedure was performed in a manner similar to Example 2. Thus, 4.29 g (yield, 62%) of Compound 39 was obtained as light yellow needles.

Melting point: 210.2-211.8°C (acetonitrile)

Elemental analysis: as $C_{21}H_{19}N_7O \cdot 0.1H_2O$			
Found (%) :	C 65.31	H 4.87	N 24.92
Calcd. (%):	C 65.14	H 5.00	N 25.32

IR (KBr) νmax (cm^{-1}): 1728, 1714, 1641

^{1}H-NMR (DMSO-d_6) δ (ppm) : 8.70(d, 1H, J=5.8Hz), 8.36 (s, 1H), 7.72(d, 1H, J=5.8Hz), 7.55-7.50(m, 2H), 7.40-7.25(m, 3H), 5.68(s, 2H), 4.06(t, 2H), 1.85-1.65(m, 2H), 0.90(t, 3H)

Example 40

6,9-Dihydro-6,9-di-n-propyl-3-(4-pyridyll-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 40):

Except that 2.50 g (8.50 mmol) of Compound t in Reference Example 18 and 1.40 g (10.2 mmol) of isonicotinic hydrazide were used, the procedure was performed in a manner similar to Example 2. Thus, 2.38 g of (yield, 83%) Compound 40 (free form) was obtained as light yellow needles.

Melting point: 198.0-200.1°C (isopropanol)

Elemental analysis: as $C_{17}H_{19}N_7O$			
Found (%) :	C 60.29	H 5.80	N 29.30
Calcd. (%):	C 60.52	H 5.68	N 29.06

IR (KBr) νmax (cm^{-1}) 1715, 1647

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.76(d, 2H, J=5.2Hz), 7.72(d, 2H, J=5.2Hz), 7.66(s, 1H), 4.46(t, 2H), 4.24(t, 2H), 2.20-2.08(m, 2H), 1.98-1.80(m, 2H), 1.05-0.98(m, 6H)

After 2.00 g (5.93 mmol) of free form of Compound 40 was suspended in 20 ml of methanol, 5 ml of hydrochloride-saturated ethanol was added to the suspension. The suspension was stirred for 10 minutes, and the solvent was evaporated under reduced pressure. Recrystallization from ethanol gave 1.48 g of Compound 40 (yield, 67%) as yellow needles.

Melting point: 193.8-199.0°C

Elemental analysis: as $C_{17}H_{19}N_7O \cdot HCl$			
Found (%):	C 54.71	H 5.64	N 26.50
Calcd. (%):	C 54.62	H 5.39	N 26.23

IR (KBr) νmax (cm^{-1}): 1710, 1652, 1632, 1592

^{1}H-NMR ($CDCl_3$) δ (ppm) : 8.86(d, 2H, J=6.9Hz) , 8.50(d, 2H, J=6.9Hz), 7.76(s, 1H), 4.49(d, 2H), 4.29(d, 2H), 2.20-1.80(m, 4H), 1.05-0.95(m, 6H)

Example 41

9-Methyl-6-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound 41):

After 24 ml of dimethylsulfoxide and 1.23 g (11.8 mmol) of ethyl carbazate were added to 2.35 g (9.87 mmol) of Compound a prepared in Reference Example 1, the mixture was stirred at 160°C for 2 hours. After cooling, 200 ml of water was added to the mixture. The precipitates were collected by filtration and recrystallized from ethanol to afford 1.10 g (yield, 45%) of Compound 41 as a white powder.

Melting point: 299.3-301.1°C (ethanol)

Elemental analysis: as $C_{10}H_{12}N_6O_2$			
Found (%):	C 48.21	H 4.73	N 33.92
Calcd. (%) :	C 48.38	H 4.87	N 33.85

IR (KBr) vmax (cm^{-1}) : 1757, 1653

^{1}H-NMR (DMSO-d_6) δ (ppm): 11.99(S, 1H), 7.91(s, 1H), 3.90(t, 2H), 3.86(s, 3H), 1.80-1.60(m, 2H), 0.87 (t, 3H)

Example 42

6-Benzyl-9-methyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound 42):

The procedure was performed in a manner similar to Example 41 except for using 2.0 g (7.0 mmol) of Compound h prepared in Reference Example 8 and 870 mg (8.4 mmol) of ethyl carbazate. Thus, 1.83 g (yield, 80%) of Compound 42 was obtained as light yellow needles.

Melting point: 295°C (dioxane-water)

Elemental analysis: as $C_{14}H_{12}N_6O_2$			
Found (%) :	C 56.51	H 3.79	N 28.47
Calcd. (%):	C 56.74	H 4.09	N 28.37

IR (KBr) vmax (cm^{-1}): 1772, 1760, 1694, 1640

^{1}H-NMR (DMSO-d_6) δ (ppm): 11.99(brs, 1H), 7.90(s, 1H), 7.42-7.25(m, 5H), 5.13(s, 2H), 3.87(s, 3H)

Example 43

8-Cyclopentyl-6-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound 43):

The procedure was performed in a manner similar to Example 41 except for using 1.50 g (5.14 mmol) of Compound e obtained in Reference Example 5 and 640 mg (6.17 mmol) of ethyl carbazate. Thus, 571 mg (yield, 37%) of Compound 43 was obtained as white needles.

Melting point: 297.1-298.8°C (dioxane-water)

Elemental analysis: as $C_{14}H_{18}N_6O_2 \cdot 0.1C_4H_8O_2$			
Found (%):	C 55.27	H 6.08	N 26.82
Calcd. (%):	C 55.59	H 6.09	N 27.01

IR (KBr) vmax (cm^{-1}): 1751, 1694, 1654

^{1}H-NMR (DMSO-d_6) δ (ppm): 13.09(brs, 1H), 11.81(s, 1H), 3.91(t, 2H), 3.27-3.13(m, 1H), 2.10-1.60(m, 10H), 0.89(t, 3H)

Example 44

6,9-Di-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound 44):

The procedure was performed in a manner similar to Example 41 except for using 1.88 g (7.07 mmol) of Compound o prepared in Reference Example 13 and 0.880 g (8.48 mmol) of ethyl carbazate. Thus, 1.65 g (yield, 85%) of Compound 44 was obtained as white needles.

Melting point: 216.7-218.0°C (isopropanol)

Elemental analysis: as $C_{12}H_{16}N_6O_2 \cdot 0.1C_3H_8O$			
Found (%) :	C 52.34	H 5.84	N 29.91
Calcd. (%):	C 52.33	H 6.00	N 29.77

IR (KBr) vmax (cm^{-1}): 1768, 1647

^{1}H-NMR ($CDCl_3$) δ (ppm): 10.85(brs, 1H), 7.51(s, 1H), 4.17(t, 2H), 4.10(t, 2H), 2.05-1.80(m, 4H), 1.00(t, 3H), 0.98(t, 3H)

Example 45

6-n-Propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound 45):

The procedure was performed in a manner similar to Example 41 except for using 3.98 g (11.6 mmol) of Compound f obtained in Reference Example 6 and 1.45 g (13.9 mmol) of ethyl carbazate. Thus, 1.05 g (yield, 19%) of 2,9-dibenzyloxymethyl-6-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound mj) was obtained as a light yellow powder.

Melting point: 88.9-90.3°C

IR (KBr) vmax.(cm^{-1}): 1764, 1700, 1653

^{1}H-NMR ($CDCl_3$) δ (ppm) : 7.57(s, 1H), 7.40-7.10(m, 10H), 5.66(s, 2H), 5.33(s, 2H), 4.69(s-like, 4H), 4.05 (t, 2H), 2.00-1.60(m, 2H), 1.00(t, 3H)

MS (m/e: relative intensity): 474(M^+, 28), 414(35), 225(7), 91(100)

After 739 mg (1.56 mmol) of Compound mj was suspended in 40 ml of toluene, 4.18 ml (4.18 mmol) of a solution of 1 M boron tribromide/methylene chloride was dropwise added to the suspension at -78°C. The mixture was stirred at 0°C for an hour. The mixture was poured onto ice water. 2 N sodium hydroxide aqueous solution was added to adjust to pH 7.5. The mixture was washed 3 times with chloroform. After the aqueous layer was concentrated under reduced pressure, the residue was purified by 200 ml of DIAION HP-40 (manufactured by Mitsubishi Chemical Industry Co., Ltd.) to give 312 mg (yield, 85%) of Compound 45 as white needles.

Melting point: >290°C (dioxane-water)

Elemental analysis: as $C_9H_{10}N_6O_2 \cdot 0.1C_4H_8O_2$			
Found (%):	C 46.36	H 4.23	N 34.51
Calcd. (%):	C 46.46	H 4.48	N 34.58

IR (KBr) vmax (cm^{-1}): 1744, 1700, 1649

^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.52(brs, 1H), 11.87(s, 1H), 7.92(s, 1H), 3.94(t, 2H) , 1.80-1.60(m, 2H), 0.90(t, 3H)

Example 46

9-Methyl-6-n-propyl-2,2,6,9-tetrahydro-3-thioxo-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 46):

After 800 mg (3.60 mmol) of Compound n prepared in Reference Example 12 was dissolved in 36 ml of pyridine, 3.6 ml of carbon disulfide was added to the solution. The mixture was refluxed for 1.5 hours under heating. After the solvent was evaporated under reduced pressure, 50 ml of toluene was added to the residue. The solvent was reevaporated under reduced pressure, and the residue was triturated with ether. Recrystallization from acetic acid gave 920 mg (yield, 97%) of Compound 46 as light yellow needles.

Melting point: 275.1-276.8°C

Elemental analysis: as $C_{10}H_{12}N_6OS \cdot 0.5C_2H_4O_2$			
Found (%) :	C 44.87	H 4.63	N 28.52
Calcd: (%):	C 44.89	H 4.79	N 28.55

IR (KBr) vmax (cm^{-1}) : 1726, 1668

^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.96(brs, 1H), 7.93(s, 1H), 3.93(t, 2H), 3.89(s, 3H), 2.00-1.45(m, 2H), 0.90 (t, 3H)

Example 47

6-Benzyl-9-methyl-2,3,6,9-tetrahydro-3-thioxo-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 47):

The procedure was performed in a manner similar to Example 46 except for using 1.50 g (5.56 mmol) of Compound p prepared in Reference Example 14. Thus, 1.14 g (yield, 66%) of Compound 47 was obtained as a light yellow powders.

Melting point: 277.5-278.4°C (dioxane)

Elemental analysis: as $C_{14}H_{12}N_6OS \cdot 0.4C_4H_8O_2 \cdot 0.3H_2O$			
Found (%):	C 53.11	H 4.10	N 23.81
Calcd. (%):	C 53.08	H 4.51	N 23.81

IR (KBr) vmax (cm^{-1}): 1730, 1673

^{1}H-NMR (DMSO-d_6) δ (ppm) : 7.96(brs, 1H), 7.50-7.15(m, 5H), 5.17(s, 2H), 3.90(s, 3H) MS (m/e: relative intensity): 312(M^+, 53), 91(100)

Example 48

2-Ethyl-9-methyl-6-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-2,5-dione (Compound 48):

After 1.60 g (6.45 mmol) of Compound 41 prepared in Example 41 was dissolved in 16 ml of N,N-dimethylformamide, 310 mg (7.74 mmol) of 60% sodium hydride was added to the solution under ice cooling. The mixture was stirred for 10 minutes. After 1.55 ml (19.4 mmol) of ethyl iodide was added under ice cooling, the mixture was stirred at 60°C for 30 minutes. After concentration of the solution, 50 ml of water was added and the mixture was extracted 3 times with 30 ml of chloroform. The extracts were combined and washed with a saturated aqueous sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluting solvent: 3% methanol/chloroform) and recrystallized from toluene to give 820 mg (yield, 46%) of Compound 48 as light yellow needles.

Melting point: 238.1-239.7°C (toluene)

Elemental analysis: as $C_{12}H_{16}N_6O_2 \cdot 0.1H_2O$			
Found (%):	C 51.74	H 5.74	N 30.21
Calcd. (%):	C 51.83	H 5.87	N 30.22

IR (KBr) vmax (cm^{-1}): 1746, 1696, 1650, 1413

^{1}H-NMR (DMSO-d_6) δ (ppm): 7.92(s, 1H), 3.91(t, 2H), 3.88(s, 3H), 3.78(q, 2H), 1.78-1.62(m, 2H), 1.26 (t, 3H), 0.89(t, 3H)

Example 49

6-Benzyl-2-ethyl-9-methyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-2,5-dione (Compound 49):

The procedure was performed in a manner similar to Example 48 except for using 1.20 g (4.05 mmol) of Compound 42 obtained in Example 42. Thus, 1.32 g (yield, 100%) of Compound 49 was obtained as white needles.

Melting point: 260.0-261.1°C (ethanol)

Elemental analysis: as $C_{16}H_{16}N_6O_2 \cdot 0.2H_2O$			
Found (%) :	C 58.63	H 4.95	N 25.73
Calcd. (%):	C 58.60	H 5.04	N 25.63

IR (KBr) vmax (cm^{-1}): 1771, 1755, 1695, 1650

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.60-7.10(m, 5H), 7.41(s, 1H), 5.22(s, 2H), 3.90(s, 3H), 3.87(q, 2H), 1.32(t, 3H)

Example 50

3-Amino-6,9-dihydro-9-methyl-6-n-propyl-5H-1,2,4-triazolo[3,4-i]purin-5-one (Compound 50):

After 756 mg (3.40 mmol) of Compound n obtained in Reference Example 12 was dissolved in 10 ml of methanol, 400 mg (3.75 mmol) of cyanogen bromide was added to the solution. The mixture was refluxed for 2 hours under heating. After the mixture was neutralized with saturated aqueous sodium bicarbonate solution, the precipitates were collected by filtration and washed with water to afford 670 mg (yield, 80%) of Compound 50 as a light yellow powder.

Melting point: >270°C (decomposed)
IR (KBr) vmax (cm^{-1}): 1698, 1666, 1616, 1323
^{1}H-NMR (90MHz; DMSO-d_6) δ (ppm): 7.85(s, 1H), 6.63 (brs, 2H), 3.97(t, 2H), 3.93(s, 3H), 2.00-1.50 (m, 2H), 0.91(t, 3H)
MS (m/e; relative intensity): 247(M^+, 100), 205(64), 204(75), 149(23)

Example 51

6-n-Butyl-9-methyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione (Compound 51):

1.71 g of Compound 51 as a white powder was obtained (yield, 82%) from 2.0 g (7.94 mmol) of Compound u obtained in Reference Example 19 by the similar method to Example 41.
Melting point: 262.1-264.5°C (acetic acid)

Elemental analysis: as $C_{11}H_{14}N_6O_2$			
Found (%):	C 50.40	H 5.59	N 32.12
Calcd. (%):	C 50.37	H 5.38	N 32.04

IR (KBr) vmax (cm^{-1}): 1754, 1698, 1652
^{1}H-NMR (DMSO-d_6) δ (ppm): 11.95(brs, 1H), 7.90(s, 1H), 3.94(t, 2H), 3.86(s, 3H), 1.75-1.60(m, 2H), 1.40-1.25 (m, 2H), 0.90(t, 3H)

Reference Example 1

3,7-Dihydro-7-methyl-6-methylthio-3-n-propyl-2H-purin-2-one (Compound a):

In an argon atmosphere, 10.7 g (268 mmol) of 60% sodium hydride was washed with n-hexane 3 times. The solvent was evaporated under reduced pressure and dried. Under ice cooling, 300 ml of N,N'-dimethylformamide was added and a suspension of 28.2 g (134 mmol) of 3-n-propyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86) in 200 ml of N,N'-dimethylformamide was dropwise added to the mixture. The mixture was incubated for 15 minutes, and 25.1 ml (403 mmol) of methyl iodide was dropwise added. After stirring for 30 minutes, 50 ml of ethanol was added to the mixture followed by concentration. Then 250 ml of water was added to the concentrate. The precipitates were collected by filtration to give 25.9 g (yield, 81%) of Compound a.
Melting point: 224.7-226.4°C (acetonitrile)

Elemental analysis: as $C_{10}H_{14}N_4OS$

Found (%): C 50.30 H 5.95 N 23.35
Calcd. (%): C 50.40 H 5.92 N 23.51

IR (KBr) vmax (cm^{-1}): 1630, 1596, 1557, 1393
^{1}H-NMR ($CDCl_3$) δ (ppm): 7.53(s, 1H), 4.16(t, 2H), 4.01 (s, 3H), 2.71(s, 3H), 1.95-1.77(m, 2H), 0.98(t, 3H)
^{13}C-NMR ($CDCl_3$) δ (ppm): 160.9, 154.7, 151.6, 143.3, 114.3, 45.0, 34.7, 21.2, 12.2, 11.2

Reference Example 2

3,7-Dihydro-6-methylthio-3-n-propyl-2H-purin-2-one (Compound b):

In an argon atmosphere, 9.77 g (244 mmol) of 60% sodium hydride was washed with n-hexane 3 times. The solvent was evaporated under reduced pressure and dried. After 900 ml of N,N'-dimethylformamide was added 57.0 g (271 mmol) of 3-n-propyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86) was gently added under ice cooling. 15 minutes after, 15.2 ml (244 mmol) of methyl iodide was dropwise added to the reaction mixture. After stirring for 30 minutes, 50 ml of ethanol was added and the mixture was concentrated under reduced pressure. Then 400 ml of water was added and precipitates were collected by filtration to give 13.9 g (yield, 23%) of

Compound b as light yellow powder. The filtrate was extracted 5 times with 200 ml of chloroform. After washing with a saturated aqueous sodium chloride solution, the extract was dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: 10% methanol/chloroform) to give further 16.0 g (yield, 26%) of Compound b as a light yellow powder.

Melting point: 240.8-242.5°C

IR (KBr) vmax (cm^{-1}): 3400(br), 1600, 1588, 1572

^{1}H-NMR (DMSO-d_6) δ (ppm): 13.54(brs, 1H), 8.13(brs, 1H), 3.99(t, 2H), 2.57(s, 3H), 1.80-1.62(m, 2H), 0.88(t, 3H)

^{13}C-NMR (DMSO-d_6) δ (ppm) : 11.0, 11.3, 20.6, 44.4, 112.8(br), 141.9(br), 149.4(br), 153.8, 160.6(br)

MS (m/e; relative intensity): 224(M^+, 36), 195(13), 182(100), 135(43)

Reference Example 3

8-Cyclopentyl-3-n-propylxanthine (Compound c):

After 30 g (163 mmol) of 5,6-diamino-1-propyl-2,4-(1H,3H)-pyrimidinedione (Japanese Published Unexamined Patent Application No. 57517/80) was suspended in 600 ml of N,N'-dimethylformamide, 17.7 ml (163 mmol) of cyclopentanecarboxylic acid, 30.0 g (196 mmol) of hydroxybenztriazole and 50.5 g (245 mmol) of dicyclohexylcarbodiimide were added to the suspension. The mixture was stirred at room temperature overnight. After insoluble materials were filtered off, the filtrate was evaporated under reduced pressure. To the residue was added 600 ml of 4 N sodium hydroxide aqueous solution and the solution was refluxed for 10 minutes under heating. After ice cooling, insoluble materials were filtered off and 50 ml of methanol was added. The resulting mixture was neutralized with conc. hydrochloric acid. The precipitates were collected by filtration to afford 28.3 g (yield, 66%) of Compound c as a white powder.

Melting point: 311.3-313.1°C (dimethylformamide)

Elemental analysis: as $C_{13}H_{18}N_4O_2$			
Found (%):	C 59.56	H 6.96	N 21.69
Calcd. (%):	C 59.52	H 6.92	N 21.36

IR (KBr) vmax (cm^{-1}): 3150, 2880, 1698, 1669

^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.05(brs, 1H), 10.94(s, 1H), 3.86(t, 2H), 3.18-3.04(m, 1H), 2.05-1.55(m, 10H), 0.87(t, 3H)

^{13}C-NMR (DMSO-d_6) δ (ppm): 157.7, 154.3, 150.9, 149.4, 106.5, 43.3, 39.0, 31.9, 25.0, 20.9, 10.9

Reference Example 4

8-Cyclopentyl-3-n-propyl-6-thioxanthine (Compound d) :

14.1 g (53.8 mmol) of Compound c obtained in Reference Example 3 and 19.5 g (87.7 mmol) of phosphorous pentasulfide in 280 ml of pyridine was refluxed for 4 hours under heating. The reaction mixture was poured onto 600 ml of ice water and the precipitates were collected by filtration. The filtrate was concentrated under reduced pressure and the precipitates were taken out by filtration. The collected precipitates were combined and 400 ml of 2 N sodium hydroxide aqueous solution was added to remove insoluble matters. After neutralization with conc. hydrochloric acid, the precipitates were collected by filtration to give crude Compound d. The crude product was recrystallized from ethanol-water to give 13.5 g (yield, 90%) of Compound d as a light yellow plate.

Melting point: 214.3-215.9°C

Elemental analysis: as $C_{13}H_{18}N_4OS \cdot 1/4C_2H_5OH$			
Found (%) :	C 56.17	H 6.76	N 19.44
Calcd. (%):	C 55.93	H 6.78	N 19.33

IR (KBr) vmax (cm^{-1}): 2960, 1663, 1605, 1510, 1403

^{1}H-NMR (DMSO-d_6) δ (ppm) : 13.03(brs, 1H), 12.04(brs, 1H), 3.90(t, 2H), 3.30-3.10(m, 1H), 2.05-1.55 (m, 10H), 0.87(t, 3H)

^{13}C-NMR (DMSO-d_6) δ (ppm) : 173.3, 161.5, 148.9, 145.7, 118.5, 56.0, 43.8, 38.7, 32.0, 25.2, 20.7, 18.5, 10.9

Reference Example 5

8-Cyclopentyl-3,7-dihydro-6-methylthio-3-n-propyl-2H-purin-2-one (Compound e):

The procedure was performed in a manner similar to Reference Example 2 except for using 6.00 g (21.6 mmol) of Compound d obtained in Reference Example 4. Thus, 4.70 g (yield, 75%) of Compound e was obtained as light yellow needles.

Melting point: 257.5-259.2°C

Elemental analysis: as $C_{14}H_{20}N_4OS$			
Found (%):	C 57.77	H 7.22	N 19.36
Calcd. (%):	C 57.51	H 6.89	N 19.16

IR (KBr) vmax (cm^{-1}): 1599, 1580, 1553, 1513

^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm): 4.24(t, 2H), 3.53-3.15 (m, 1H), 2.10(s, 3H), 2.50-1.50(m, 10H), 0.95(t, 3H)

Reference Example 6

7-Benzyloxymethyl-3,7-dihydro-6-methylthio-3-n-propyl-2H-purin-2-one (Compound f):

After 224 mg (1.0 mmol) of Compound b obtained in Reference Example 2 was dissolved in 2 ml of N,N'-dimethylformamide, 48.0 mg (1.2 mmol) of 60% sodium hydride was added to the mixture under ice cooling. 15 minutes after, 209 µl (1.5 mmol) of benzyl chloromethyl ether was added to the mixture. The mixture was stirred for an hour, poured onto 10 ml of water, and extracted 3 times with 5 ml of chloroform. After washing with a saturated aqueous sodium chloride solution, the extracts were dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was triturated with ether to give 223 mg (yield, 65%) of Compound f as a white powder.

Melting point: 166.8-168.3°C

Elemental analysis: as $C_{17}H_{20}N_4O_2S$			
Found (%):	C 58.99	H 5.80	N 16.22
Calcd. (%):	C 59.28	H 5.85	N 16.27

IR (KBr) vmax (cm^{-1}): 1623, 1592, 1556

^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm) : 7.58(s, 1H), 7.29(s, 5H), 5.61(s, 2H), 4.59(s, 2H), 4.12(t, 2H), 2.70 (s, 3H), 2.00-1.60(m, 2H), 0.99(t, 3H)

MS (m/e; relative intensity): 344(M^+, 19), 302(9), 211(10), 181(10), 91(100)

Reference Example 7

3-Benzyl-6-thioxanthine (Compound g):

The procedure was performed in a manner similar to Reference Example 4 except for using 31.0 g (128 mmol) of 3-benzylxanthine [Biochemistry, 16, 3316 (1977)]. Thus, 28.7 g (yield, 87%) of Compound g was obtained as a light yellow powder.

Melting point: 261.8-263.1°C (DMSO-water)

IR (KBr) vmax (cm^{-1}): 1682, 1600, 1560, 1426

^{1}H-NMR (90MHz; DMSO-d_6) δ (ppm) : 13.4(brs, 1H), 12.2 (brs, 1H), 7.99(s, 1H), 7.50-7.05(m, 5H), 5.12 (s, 2H)

Reference Example 8

3-Benzyl-3,7-dihydro-7-methyl-6-methylthio-2H-purin-2-one (Compound h) and 3-benzyl-3,7-dihydro-6-methylthio-2H-purin-2-one (Compound i):

The procedure was performed in a manner similar to Reference Example 2 except for using 14 g (54.3 mmol) of compound g obtained in Reference Example 7. The crude product was purified by silica gel column chromatography and a product was eluted with 5% methanol/chloroform. Concentration of the elution (5% methanol/chloroform) gave

5.86 g (yield, 40%) of Compound h as a light yellow powder.
Melting point: 268.1-269.8°C

Elemental analysis: as $C_{13}H_{12}N_4OS$			
Found (%):	C 57.42	H 4.13	N 20.14
Calcd. (%):	C 57.34	H 4.44	N 20.57

IR (KBr) vmax (cm^{-1}): 3420(br), 1600, 1566, 1543
^{1}H-NMR (90MHz; DMSO-d_6) δ (ppm): 13.50(brs, 1H), 8.07(s, 1H), 7.45-7.05(m, 5H), 5.22(s, 2H), 2.60(s, 3H)
MS (m/e: relative intensity): 272(M^+, 53), 257(11), 225(18), 91(100), 65(18)

Concentrating of the elution (2% methanol/chloroform) fraction eluted by silica gel column chromatography afforded 7.24 g of the residue. The procedure was performed in a manner similar to Reference Example 1 except that 7.24 g of the residue was used. Thus, 5.13 g (yield, 33%) of Compound i was obtained as a light yellow powder.
Melting point: 214.8-216.4°C
IR (KBr) vmax (cm^{-1}): 1633, 1591. 1558
^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm): 7.47(s, 1H), 7.60-7.05(m, 5H), 5.32(s, 2H), 3.82(s, 3H), 2.67(s, 3H)
MS (m/e: relative intensity): 286(M^+, 97), 271(40), 228(50),211(17), 195(19), 91(100)

Reference Example 9

3-Phenyl-6-thioxanthine (Compound j):

The procedure was performed in a manner similar to Reference Example 4 except for using 23.8 g (104 mmol) of 3-phenylxanthine [Chem. Pharm. Bull., 14, 1365 (1966)]. Thus, 19.9 g (yield, 78%) of Compound j was obtained as a light yellow powder.
Melting point: >290°C
IR (KBr) vmax (cm^{-1}): 1682, 1595, 1587, 1415
^{1}H-NMR (90MHz; DMSO-d_6) δ (ppm): 7.94(s, 1H), 7.60-7.30(m, 5H)

Reference Example 10

3,7-Dihydro-7-methyl-6-methylthio-3-phenyl-2H-purin-2-one (Compound k) and 3,7-dihydro-9-methyl-6-methylthio-2H-purin-2-one (Compound ℓ):

The procedure was performed in a manner similar to Reference Example 1 except for using 9.89 g (40.5 mmol) of Compound g obtained in Reference Example 7. The crude product was purified by silica gel column chromatography (eluent: 1% methanol/chloroform). Thus, 7.75 g (yield, 74%) of Compound k and 1.62 g (yield, 16%) of Compound ℓ were obtained as a light yellow powder.
Physicochemical properties of Compound k are as follows.
Rf: 0.55 [TLC plate: silica gel $60F_{254}$ (layer thickness of 0.25 mm, manufactured by Merck), developing solvent: 10% methanol/chloroform]
Melting point: 261.1-262.8°C
IR (KBr) vmax (cm^{-1}): 1640, 1571, 1555
^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm): 7.48(s, 1H), 7.60-7.30(m, 5H), 4.01(s, 3H), 2.75(s, 3H)
Physicochemical properties of Compound ℓ are as follows.
Rf: 0.46 [TLC plate: silica gel $60F_{254}$ (layer thickness of 0.25 mm, manufactured by Merck), developing solvent: 10% methanol/chloroform]
IR (KBr) vmax (cm^{-1}): 1660, 1556, 1371
^{1}H-NMR ($CDCl_3$) δ (ppm): 7.62-7.50(m, 3H), 7.45-7.37(m, 2H), 7.27(s, 1H), 2.94(s, 3H), 2.69(s, 3H)
^{13}C-NMR ($CDCl_3$) δ (ppm): 171.2, 153.8, 139.6, 138.8, 135.2, 130.1, 130.0, 129.1, 122.2, 33.0, 11.9
MS (m/e: relative intensity): 272(M^+, 96), 225(88), 198(14), 104(17), 77(28), 42(100)

Reference Example 11

3-Benzyl-7-benzyloxymethyl-3,7-dihydro-6-methylthio-2H-purin-2-one (Compound m):

The procedure was performed in a manner similar to Reference Example 4 except that 7.00 g (25.7 mmol) of

Compound f obtained in Reference Example 6 was used. Thus, 9.15 g (yield, 91%) of Compound m was obtained as a white powder.

Melting point: 193.7-195.2°C

IR (KBr) vmax (cm^{-1}) : 1641, 1625, 1586. 1555

^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm) : 7.59(s, 1H), 7.65-7.15(m, 10H), 5.60(s, 2H), 5.36(s, 2H), 4.58(s, 2H), 2.69 (s, 3H)

Reference Example 12

3,7-Dihydro-6-hydrazino-7-methyl-3-n-propyl-2H-purin-2-one (Compound n):

After 50 ml of hydrazine monohydrate was added to 5.00 g (21.0 mmol) of Compound a prepared in Reference Example 1, the mixture was stirred at room temperature for 2 days. The precipitates were collected by filtration and washed with isopropanol to give 4.04 g (yield, 87%) as a white powder.

Melting point: 180.1-181.9°C

IR (KBr) vmax (cm^{-1}) : 1673

^{1}H-NMR (90MHz; $CDCl_3$) δ (ppm) : 7.25(s, 1H), 3.92(t, 2H), 3.87(s, 3H), 2.00-1.55(m, 2H), 0.97(t, 3H)

MS (m/e: relative intensity): 222(M^+, 100), 193(13), 180(49), 179(22)

Reference Example 13

3,7-Dihydro-3,7-di-n-propyl-6-methylthio-2H-purin-2-one (Compound o):

2.00 g (8.93 mmol) of Compound b obtained in Reference Example 2 was gently added to a suspension of 356 mg (8.93 mmol) of 60% sodium hydride in 20 ml of N,N-dimethylformamide at 0°C. 10 minutes after, 2.64 ml (27.0 mmol) of propyl iodide was gently added to the mixture. The mixture was stirred at room temperature for 2 hours and a half. After 150 ml of saturated ammonium chloride aqueous solution was added to the reaction solution, the mixture was extracted 3 times with chloroform. The extracts were combined and washed twice with a saturated aqueous sodium chloride. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. 50% ether/ n-hexane was added to the residue. The precipitates were taken out by filtration to give 2.09 g (yield, 84%) of Compound o as a light yellow powder.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.53(s, 1H), 4.22(t, 2H), 4.14 (t, 2H), 2.70(s, 3H), 2.20-1.65(m, 4H), 1.15-0.90 (m, 6H)

Reference Example 14

3-Benzyl-3,7-dihydro-6-hydrazino-7-methyl-2H-purin-2-one (Compound p):

After 16.0 ml of hydrazine hydrate was added to 2.00 g (6.99 mmol) of Compound h prepared in Reference Example 8, the mixture was stirred at room temperature for day and night. The reaction mixture was poured onto 300 ml of water and the precipitates were taken out by filtration and washed with ether to give 1.60 g (yield, 85%) of Compound p as a white powder.

Melting point: 180.0-181.9°C

MS (m/e; relative intensity): 222(M^+, 100), 180(52)

^{1}H-NMR DMSO-d_6) δ (ppm) : 7.78(s, 1H), 7.50-7.10(m, 5H), 5.03(s, 2H), 3.80(s, 3H)

Reference Example 15

3-n-Butyl-3,7-dihydro-6-methylthio-2H-purin-2-one (Compound q)

7.88 g of Compound q (yield, 41%) was obtained from 18.2 g (81.0 mmol) of 3-n-butyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86), by the similar method to Reference Example 2 as a yellow powder.

Elemental analysis: as $C_{16}H_{14}N_4OS$			
Found (%):	C 50.22	H 6.02	N 23.67
Calcd. (%):	C 50.40	H 5.92	N 23.51

^{1}H-NMR (DMSO-d_6; 90MHz) δ(ppm): 8.05(s, 1H), 4.00(t, 2H), 2.56(s, 3H), 1.85-1.05(m, 4H), 0.89(t, 3H)
MS (m/e: relative intensity): 238(M^+, 38), 196(100), 182(73), 135(60)

Reference Example 16

7-Benzyloxymethyl-3-n-butyl-3,7-dihydro-6-methylthio-2H-purin-2-one (Compound r):

4.83 g of Compound r (yield, 85%) as a white powder was obtained from 3.78 g (15.9 mmol) of Compound g in Reference Example 15, by the method similar to Reference Example 6.
^{1}H-NMR ($CDCl_3$: 90MHz) δ (ppm) : 7.58(s, 1H), 7.28(brs, 5H), 5.60(s, 2H), 4.59(s, 2H), 4.17(t, 2H), 2.70 (s, 3H), 1.90-1.15(m, 4H), 0.95(t, 3H)
MS (m/e: relative intensity): 358(M^+, 14), 316(26), 91(100)

Reference Example 17

7-Benzyl-6-benzylthio-3,7-dihydro-3-n-propyl-2H-purin-2-one (Compound s)

8.30 g of Compound s (yield, 89%) as a white powder was obtained from 5.00 g (23.8 mmol) of 3-n-propyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86) and 7.08 ml (59.5 mmol) of benzyl bromide, by the similar manner to Reference Example 1.
^{1}H-NMR ($CDCl_3$; 90MHz) δ (ppm): 7.48(s, 1H), 7.50-7.00(m, 10H), 5.41(s, 2H), 4.60(s, 2H), 4.16 (t, 2H), 2.05-1.60(m, 2H), 1.00(t, 3H)

Reference Example 18

3,7-Dihydro-3,7-di-n-propyl-6-n-propylthio-2H-purin-2-one (Compound t)

3.15 g of Compound t (yield, 75%) as a light yellow powder was obtained from 3.00 g (14.3 mmol) of 3-n-propyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86) and 3.49 ml (35.7 mmol) of propyliodide, by similar manner to Reference Example 1.
^{1}H-NMR ($CDCl_3$; 90MHz) δ (ppm): 7.55(s, 1H), 4.30-4.00 (m, 4H), 3.38(t, 2H), 2.15-1.55(m, 6H), 1.20-0.85(m, 9H)

Reference Example 19

3-n-Butyl-3,7-dihydro-7-methyl-6-methylthio-2H-purin-2-one (Compound u):

6.33 g of Compound u (yield, 52%) as a light yellow powder was obtained from 10.7 g (47.9 mmol) of 3-n-butyl-6-thioxanthine (Japanese Published Unexamined Patent Application No. 183287/86), by the similar method to Reference Example 1.
^{1}H-NMR ($CDCl_3$; 90MHz) δ (ppm) : 7.50(s, 1H), 4.18(t, 2H), 3.98(s, 3H), 2.68(s, 3H), 1.95-1.20(m, 4H), 0.93(t, 3H)
MS (m/e; relative intensity): 252(M^+, 38), 210(100), 196(68)

Pharmaceutical preparation 1

Tablet:

A tablet having the following composition was prepared according to the conventional method.

Compound 25	20 mg
Lactose	60 mg
Potato starch	30 mg
Polyvinyl alcohol	3 mg
Magnesium stearate	1 mg

Pharmaceutical preparation 2

Powder:

A powder having the following composition was prepared according to the conventional method.

Compound 31	20 mg
Lactose	300 mg

Pharmaceutical preparation 3

Syrup:

A syrup having the following composition was prepared according to the conventional method.

Compound 41	20 mg
Refined saccharose	30 mg
Ethyl p-hydroxybenzoate	40 mg
Propyl p-hydroxybenzoate	10 mg
Strawberry flavor	0.1 ml
Water to make the total volume	100 ml

Pharmaceutical preparation 4

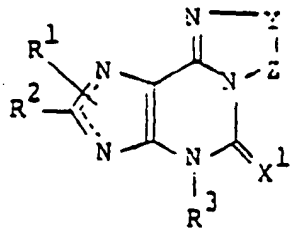
Capsule:

Ingredients set forth below were admixed and charged into gelatin capsules in accordance with the conventional method to thereby prepare a capsule.

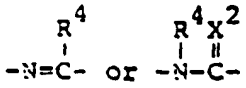
Compound 51	20 mg
Lactose	200 mg
Magnesium stearate	5 mg

Claims

1. An s-triazolo[3,4-i]purine compound represented by the formula:



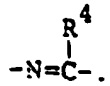
wherein Y-Z represents



where R^4 represents hydrogen, alkyl, an aromatic heterocyclic group which is optionally substituted with 1 or 2 substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen, or substituted or unsubstituted aryl;
and X^2 represents oxygen, sulfur or NH;

each of R^1 and R^2 independently represents hydrogen, alkyl, cycloalkyl, aralkyl or substituted or unsubsituted aryl;
R^3 represents alkyl, cycloalkyl, aralkyl or substituted or unsubstituted aryl;
X^1 represents oxygen or sulfur;
... represents a single bond or a double bond and substituted or unsubstituted aryl means aryl which is optionally substituted with 1 or 2 substituents independently selected from C_1-C_6 alkyl, trifluoromethyl, hydroxyl, C_1-C_6 alkoxyl, C_1-C_6 alkylthio, nitro, halogen, amino, C_1-C_6 alkylamino, C_1-C_6 alkanoylamino, aroylamino, carboxyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkanoyl and aroyl; or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein Y-Z represents



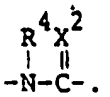
3. A compound according to claim 2, wherein R^4 is an optionally substituted aromatic heterocyclic group as defined in claim 1; each of R^1 and R^2 independently represents hydrogen, alkyl, cycloalkyl or aralkyl; R^3 represents alkyl or aralkyl; and X^1 is oxygen.

4. A compound according to claim 3, wherein R^4 is pyridyl which is optionally substituted with 1 or 2 substituents selected from C_1-C_6 alkyl, C_1-C_6 alkoxy and halogen.

5. A compound according to Claim 4, which is selected from the group consisting of

6,9-dihydro-9-methyl-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
6,9-dihydro-9-methyl-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
6,9-dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
6,9-dihydro-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
6-benzyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
6-n-butyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one;
9-benzyl-6,9-dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one; and
6,9-dihydro-6,9-di-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-one.

6. A compound according to Claim 1, wherein Y-Z represents



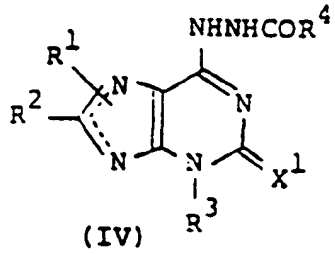
7. A compound according to Claim 6, wherein R^4 is hydrogen or alkyl; X^2 is oxygen; each of R^1 and R^2 independently represents hydrogen. alkyl or cycloalkyl; R^3 is alkyl; and X^1 is oxygen.

8. A compound according to Claim 7, which is 9-methyl-6-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione or 6-n-butyl-9-methyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dione.

9. A compound according to Claim 1, wherein said salt is selected from the group consisting of pharmaceutically acceptable acid addition salt, metal salt, ammonium salt, organic amine addition salt and amino acid addition salt.

10. A pharmaceutical composition comprising a pharmaceutical carrier and as an active ingredient, an effective amount of the compound as defined by Claim 1.

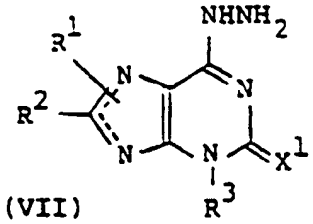
11. A process for preparing a compound according to claim 2 comprising the step of cyclization of



(IV)

wherein R^1, R^2, R^3, R^4 and X^1 are as defined in claim 1.

12. A process for preparing a compound according to claim 2 comprising the step of reacting



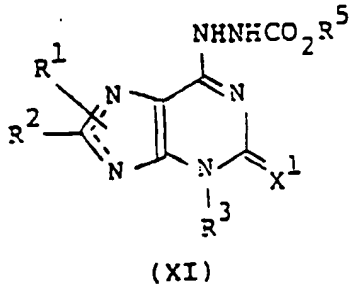
(VII)

with

$$R^4C(OR^5)_3 \qquad \text{(VIII)}$$

wherein R^1, R^2, R^3, R^4 and X^1 are as defined in claim 1 and R^5 represents alkyl having 1 to 10 carbon atoms.

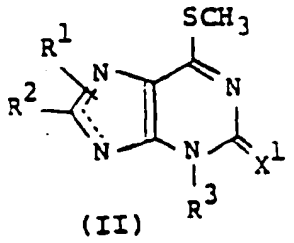
13. A process for preparing a compound according to claim 6 wherein R^4 is hydrogen and X^2 is oxygen comprising the step of cyclization of



(XI)

wherein R^1, R^2, R^3 and X^1 are as defined in claim 1 and R^5 is as defined in claim 12.

14. A process for preparing a compound according to claim 6 wherein R^4 is hydrogen and X^2 is oxygen comprising the step of reacting



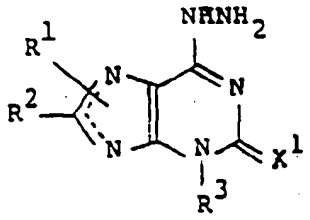
(II)

with

$$R^5O_2C\text{-}NHNH_2 \qquad (IX)$$

wherein R^1, R^2, R^3, R^5 and X^1 are as defined in claim 13.

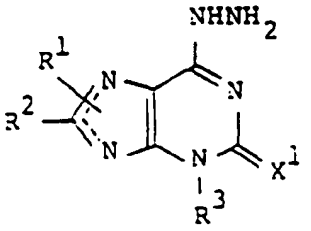
15. A process for preparing a compound according to claim 6 wherein R^4 is hydrogen and X^2 is sulfur comprising the step of reacting



(VII)

with CS_2
wherein R^1, R^2,R^3 and X^1 are as defined in claim 1.

16. A process for preparing a compound according to claim 6 wherein R^4 is hydrogen and X^2 is NH comprising the step of reacting



(VII)

with BrCN
wherein R^1, R^2, R^3 and X^1 are as defined in claim 1.

17. A process for preparing a compound according to claim 6 wherein R^4 is as defined in claim 1 with the proviso that it is different from hydrogen comprising the step of reacting

a) the product according to claim 13 or 14 with

$$R^{4a}\text{-}L$$

wherein R^{4a} is as defined as R^4 above and L is a leaving group if X^2 is oxygen

b) the product according to claim 15 with

$$R^{4a}\text{-}L$$

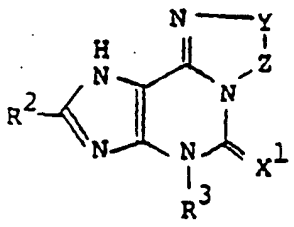
wherein R^{4a} is as defined as R^4 above and L is a leaving group if X^2 is sulfur

c) the product according to claim 16 with

$$R^{4a}\text{-}L$$

wherein R^{4a} is as defined as R^4 above and L is a leaving group if X^2 is NH.

18. A process for preparing a compound according to claim 1 wherein R^1 is as defined in claim 1 with the proviso that it is different from hydrogen comprising the step of reacting



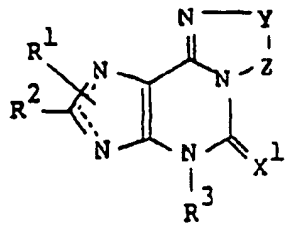
(Ic)

with R^{1a}-L

wherein R^2, R^3, X^1 and Y-Z are as defined in claim 1, and R^{1a} is as defined as R^1 above and L is a leaving group.

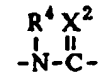
Patentansprüche

1. s-Triazolo[3,4-i]purin-Verbindung der Formel



in der Y-Z ein Rest

oder ein Rest



ist, wobei R^4 ein Wasserstoffatom, ein Alkylrest, ein aromatischer heterocyclischer Rest, der gegebenenfalls mit einem oder zwei Substituenten substituiert ist, die unabhängig aus einem C_1-C_6-Alkyl-, C_1-C_6-Alkoxyrest und einem Halogenatom ausgewählt sind oder ein substituierter oder unsubstituierter Arylrest ist;

und X^2 ein Sauerstoff-, ein Schwefelatom oder eine NH-Gruppe ist;
R^1 und R^2 jeweils unabhängig voneinander ein Wasserstoffatom, einen Alkyl-, Cycloalkyl-, Aralkyl- oder substituierten oder unsubstituierten Arylrest bedeuten;
R^3 ein Alkyl-, Cycloalkyl-, Aralkyl- oder substituierter oder unsubstituierter Arylrest ist;
X^1 ein Sauerstoff- oder Schwefelatom ist;
⋯ eine Einzel- oder eine Doppelbindung bedeutet und substituierter oder unsubstituierter Arylrest einen Arylrest bedeutet, der gegebenenfalls mit einem oder zwei Substituenten substituiert ist, die unabhängig voneinander aus einem C_1-C_6-Alkylrest, einer Trifluormethyl-, einer Hydroxylgruppe, einem C_1-C_6-Alkoxy-, C_1-C_6-Alkylthiorest, einer Nitrogruppe, einem Halogenatom, einer Aminogruppe, einem C_1-C_6-Akylamino-, C_1-C_6-Alkanoylamino-, Aroylaminorest, einer Carboxylgruppe, einem C_1-C_6-Alkoxycarbonyl-, C_1-C_6-Alkanoyl- und Aroylrest ausgewählt sind; oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, in der Y-Z einen Rest

bedeutet.

3. Verbindung nach Anspruch 2, in der R^4 ein gegebenenfalls substituierter aromatischer heterocyclischer Rest ist, wie in Anspruch 1 definiert; R^1 und R^2 jeweils unabhängig voneinander ein Wasserstoffatom, einen Alkyl-, Cycloalkyl- oder Aralkylrest bedeuten; R^3 einen Alkyl- oder Aralkylrest bedeutet; und X^1 ein Sauerstoffatom ist.

4. Verbindung nach Anspruch 3, in der R^4 eine Pyridylgruppe ist, die gegebenenfalls mit einem oder zwei Substituenten substituiert ist, die aus einem C_1-C_6-Alkyl-, C_1-C_6-Alkoxyrest und einem Halogenatom ausgewählt sind.

5. Verbindung nach Anspruch 4, ausgewählt aus

6,9-Dihydro-9-methyl-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-on;

6,9-Dihydro-9-methyl-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-on;

6,9-Dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-on;

6,9-Dihydro-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-on;

6-Benzyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-on;

6-n-Butyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-on;

9-Benzyl-6,9-dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-on; und

6,9-Dihydro-6,9-di-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purin-5-on.

6. Verindung nach Anspruch 1, in der Y-Z einen Rest

bedeutet.

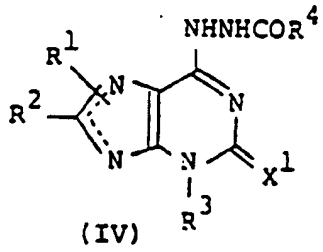
7. Verbindung nach Anspruch 6, in der R^4 ein Wasserstoffatom oder ein Alkylrest ist; X^2 ein Sauerstoffatom ist; R^1 und R^2 jeweils unabhängig voneinander ein Wasserstoffatom, einen Alkyl- oder Cycloalkylrest bedeuten; R^3 ein Alkylrest ist; und X^1 ein Sauerstoffatom ist.

8. Verbindung nach Anspruch 7, nämlich 9-Methyl-6-n-propyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dion; oder 6-n-Butyl-9-methyl-2,5,6,9-tetrahydro-3H-1,2,4-triazolo[3,4-i]purin-3,5-dion.

9. Verbindung nach Anspruch 1, wobei das Salz aus dem pharmazeutisch verträglichen Säureadditionssalz, Metallsalz, Ammoniumsalz, Additionssalz eines organischen Amins und Aminosäureadditionssalz ausgewählt ist.

10. Arzneimittel umfassend einen pharmazeutischen Träger und als Wirkstoff eine wirksame Menge der Verbindung, wie in Anspruch 1 definiert.

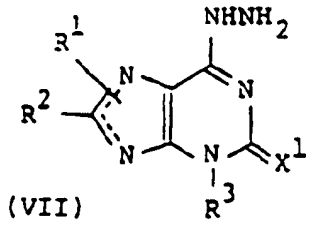
11. Verfahren zur Herstellung einer Verbindung nach Anspruch 2, umfassend die Cyclisierung von



(IV)

wobei R^1, R^2, R^3, R^4 und X^1 wie in Anspruch 1 definiert sind.

12. Verfahren zur Herstellung einer Verbindung nach Anspruch 2, umfassend die Umsetzung von



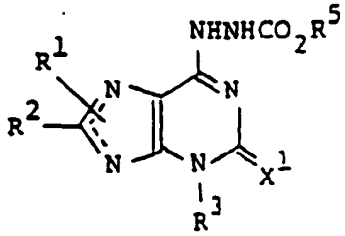
(VII)

mit

$$R^4C(OR^5)_3 \qquad \text{(VIII)}$$

wobei R^1, R^2, R^3, R^4 und X^1 wie in Anspruch 1 definiert sind und R^5 einen Alkylrest mit 1 bis 10 Kohlenstoffatomen bedeutet.

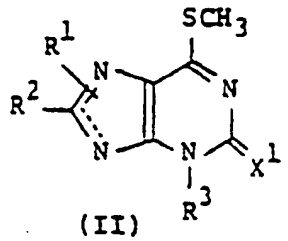
13. Verfahren zur Herstellung einer Verbindung nach Anspruch 6, wobei R^4 ein Wasserstoffatom und X^2 ein Sauerstoffatom ist, umfassend die Cyclisierung von



(IX)

wobei R^1, R^2, R^3 und X^1 wie in Anspruch 1 definiert sind und R^5 wie in Anspruch 12 definiert ist.

14. Verfahren zur Herstellung einer Verbindung nach Anspruch 6, wobei R^4 ein Wasserstoffatom und X^2 ein Sauerstoffatom ist, umfassend die Umsetzung von



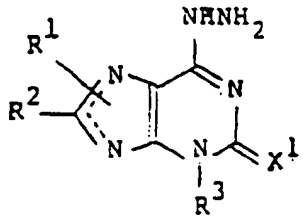
(II)

mit

$$R^5O_2C\text{-}NHNH_2 \qquad \text{(IX)}$$

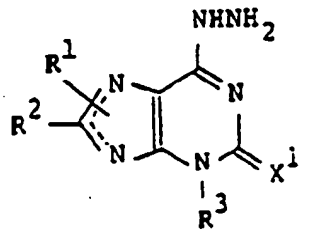
wobei R^1, R^2, R^3, R^5 und X^1 wie in Anspruch 13 definiert sind.

15. Verfahren zur Herstellung einer Verbindung nach Anspruch 6, wobei R^4 ein Wasserstoffatom und X^2 ein Schwefelatom ist, umfassend die Umsetzung von



mit CS_2
wobei R^1, R^2, R^3 und X^1 wie in Anspruch 1 definiert sind.

16. Verfahren zur Herstellung einer Verbindung nach Anspruch 6, wobei R^4 ein Wasserstoffatom und X^2 eine Gruppe NH ist, umfassend die Umsetzung von



mit BrCN
wobei R^1, R^2, R^3 und X^1 wie in Anspruch 1 definiert sind.

17. Verfahren zur Herstellung einer Verbindung nach Anspruch 6, wobei R^4 wie in Anspruch 1 definiert ist, mit der Maßgabe, daß R^4 kein Wasserstoffatom ist, umfassend die Umsetzung von

a) dem Produkt nach Anspruch 13 oder 14 mit

$$R^{4a}\text{-L},$$

wobei R^{4a} wie vorstehend R^4 definiert ist und L eine Abgangsgruppe ist, wenn X^2 ein Sauerstoffatom ist

b) dem Produkt nach Anspruch 15 mit

$$R^{4a}\text{-L},$$

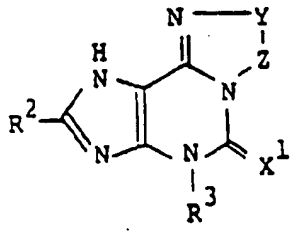
wobei R^{4a} wie vorstehend R^4 definiert ist und L eine Abgangsgruppe ist, wenn X^2 ein Schwefelatom ist

c) dem Produkt nach Anspruch 16 mit

$$R^{4a}\text{-L},$$

wobei R^{4a} wie vorstehend R^4 definiert ist und L eine Abgangsgruppe ist, wenn X^2 eine Gruppe NH ist.

18. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei R^1 wie in Anspruch 1 definiert ist, mit der Maßgabe, daß R^1 kein Wasserstoffatom ist, umfassend die Umsetzung von

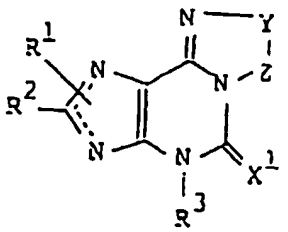


(Ic)

mit R^{1a}-L
wobei R^2, R^3, X^1 und Y-Z wie in Anspruch 1 definiert sind und R^{1a} wie vorstehend R^1 definiert ist und L eine Abgangsgruppe ist.

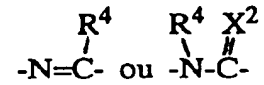
Revendications

1. Composé de type s-triazolo[3,4-i]purine, représenté par la formule suivante :



dans laquelle

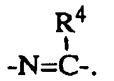
Y-Z représente



où R^4 représente un atome d'hydrogène, un groupe alkyle, un groupe hétérocyclique aromatique portant éventuellement un ou deux substituants choisis indépendamment parmi les groupes alkyle en C_{1-6}, les groupes alcoxy en C_{1-6} et les atomes d'halogène, ou un groupe aryle portant ou non des substituants, et X^2 représente un atome d'oxygène ou de soufre ou un groupe NH,
R^1 et R^2 représentent chacun, indépendamment, un atome d'hydrogène ou un groupe alkyle, cycloalkyle, aralkyle ou aryle portant ou non des substituants,
R^3 représente un groupe alkyle, cycloalkyle, aralkyle ou aryle portant ou non des substituants,
X^1 représente un atome d'oxygène ou de soufre, et
⋯ représente une liaison simple ou une liaison double,

l'expression "aryle portant ou non des substituants" désignant un groupe aryle portant éventuellement un ou deux substituants choisis indépendamment parmi les atomes d'halogène et les groupes alkyle en C_{1-6}, trifluorométhyle, hydroxy, alcoxy en C_{1-6}, alkylthio en C_{1-6}, nitro, amino, (alkyle en C_{1-6})amino, (alcanoyle en C_{1-6})amino, aroylamino, carboxy, (alcoxy en C_{1-6})carbonyle, alcanoyle en C_{1-6} et aroyle,
ou sel, admissible en pharmacie, d'un tel composé.

2. Composé conforme à la revendication 1, dans lequel Y-Z représente



3. Composé conforme à la revendication 2, dans lequel R^4 représente un groupe hétérocyclique aromatique portant éventuellement des substituants, tel qu'on l'a défini dans la revendication 1, R^1 et R^2 représentent chacun, indépendamment, un atome d'hydrogène ou un groupe alkyle, cycloalkyle ou aralkyle, R^3 représente un groupe alkyle ou aralkyle, et X^1 représente un atome d'oxygène.

4. Composé conforme à la revendication 3, dans lequel R^4 représente un groupe pyridyle qui porte éventuellement un ou deux substituants choisis parmi les atomes d'halogène et les groupes alkyle en C_{1-6} et alcoxy en C_{1-6}.

5. Composé conforme à la revendication 4, choisi parmi les suivants :

6,9-dihydro-9-méthyl-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purine-5-one,

6,9-dihydro-9-méthyl-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-i]purine-5-one,
6,9-dihydro-6-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purine-5-one,
6,9-dihydro-6-n-propyl-3-(3-pyridyl)-5H-1,2,4-triazolo[3,4-1]purine-5-one,
6-benzyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-1]purine-5-one,
6-n-butyl-6,9-dihydro-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-i]purine-5-one,
9-benzyl-6,9-dihydro-6-n-propyl-3-(4-pyridyl)-5H- 1,2,4-triazolo[3,4-i]purine-5-one, et
6,9-dihydro-6,9-di-n-propyl-3-(4-pyridyl)-5H-1,2,4-triazolo[3,4-1]purine-5-one.

6. Composé conforme à la revendication 1, dans lequel Y-Z représente

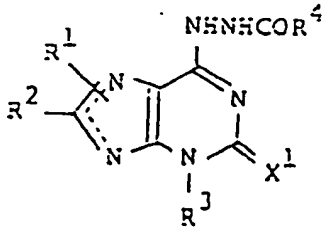
7. Composé conforme à la revendication 6, dans lequel R^4 représente un atome d'hydrogène ou un groupe alkyle, X^2 représente un atome d'oxygène, R^1 et R^2 représentent chacun, indépendamment, un atome d'hydrogène ou un groupe alkyle ou cycloalkyle, R^3 représente un groupe alkyle, et X^1 représente un atome d'oxygène.

8. Composé conforme à la revendication 7, qui est de la 9-méthyl-6-n-propyl-2,5,6,9-tétrahydro-3H-1,2,4-triazolo[3 , 4-i]purine-3,5-dione ou de la 6-n-butyl-9-méthyl-2,5,6,9-tétrahydro-3H-1,2,4-triazolo[3,4-i]purine-3,5-dione.

9. Composé conforme à la revendication 1, dans lequel ledit sel est choisi parmi les sels, admissibles en pharmacie, d'addition d'acide, de métal, d'ammonium, d'addition d'amine organique ou d'addition d'acide aminé.

10. Composition pharmaceutique comprenant un véhicule pharmaceutique et, comme ingrédient actif, une quantité efficace d'un composé conforme à la revendication 1.

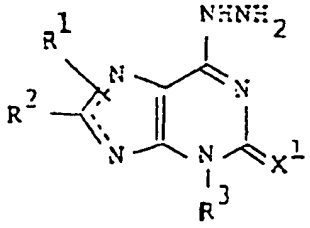
11. Procédé de préparation d'un composé conforme à la revendication 2, qui comporte une étape de cyclisation d'un composé de formule



(IV)

dans laquelle R^1, R^2, R^3, R^4 et X^1 ont les significations indiquées dans la revendication 1.

12. Procédé de préparation d'un composé conforme à la revendication 2, qui comporte une étape de réaction d'un composé de formule



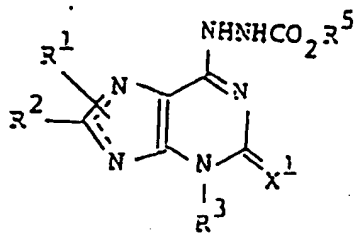
(VII)

avec un composé de formule

$$R^4C(OR^5)_3 \qquad (VIII)$$

formules dans lesquelles R^1, R^2, R^3, R^4 et X^1 ont les significations indiquées dans la revendication 1, et R^5 représente un groupe alkyle comportant de 1 à 10 atomes de carbone.

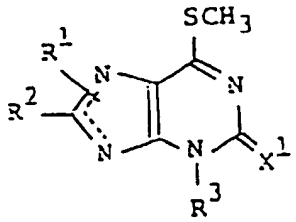
13. Procédé de préparation d'un composé conforme à la revendication 6, dans lequel R^4 représente un atome d'hydrogène et X^2 représente un atome d'oxygène, lequel procédé comporte une étape de cyclisation d'un composé de formule



(XI)

dans laquelle R^1, R^2, R^3 et X^1 ont les significations indiquées dans la revendication 1, et R^5 a la signification indiquée dans la revendication 12.

14. Procédé de préparation d'un composé conforme à la revendication 6, dans lequel R^4 représente un atome d'hydrogène et X^2 représente un atome d'oxygène, lequel procédé comporte une étape de réaction d'un composé de formule



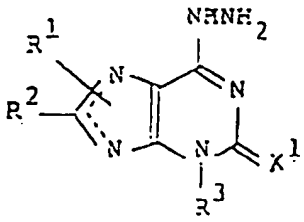
(II)

avec un composé de formule

$$R^5O_2C\text{-}NHNH_2 \qquad (IX)$$

formules dans lesquelles R^1, R^2, R^3, R^5 et X^1 ont les significations indiquées dans la revendication 13.

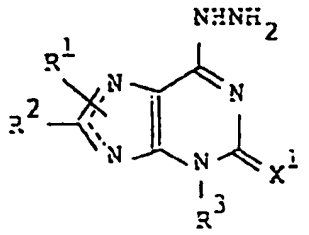
15. Procédé de préparation d'un composé conforme à la revendication 6, dans lequel R^4 représente un atome d'hydrogène et X^2 représente un atome de soufre, lequel procédé comporte une étape de réaction de CS_2 avec un composé de formule



(VII)

dans laquelle R^1, R^2, R^3 et X^1 ont les significations indiquées dans la revendication 1.

16. Procédé de préparation d'un composé conforme à la revendication 6, dans lequel R^4 représente un atome d'hydrogène et X^2 représente un groupe imino NH, lequel procédé comporte une étape de réaction de BrCN avec un composé de formule



(VII)

dans laquelle R^1, R^2, R^3 et X^1 ont les significations indiquées dans la revendication 1.

17. Procédé de préparation d'un composé conforme à la revendication 6, dans lequel R^4 a la signification indiquée dans la revendication 1, excepté celle d'un atome d'hydrogène, lequel procédé comporte,

a) dans le cas où X^2 représente un atome d'oxygène, une étape de réaction d'un produit obtenu conformément à la revendication 13 ou 14 avec un composé de formule

$$R^{4a}\text{-}L$$

où R^{4a} a la signification donnée ci-dessus pour R^4 et L représente un groupe partant,
b) dans le cas où X^2 représente un atome de soufre, une étape de réaction d'un produit obtenu conformément à la revendication 15 avec un composé de formule

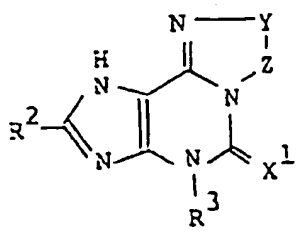
$$R^{4a}\text{-}L$$

où R^{4a} a la signification donnée ci-dessus pour R^4 et L représente un groupe partant, ou bien
c) dans le cas où X^2 représente un groupe imino NH, une étape de réaction d'un produit obtenu conformément à la revendication 16 avec un composé de formule

$$R^{4a}\text{-}L$$

où R^{4a} a la signification donnée ci-dessus pour R^4 et L représente un groupe partant.

18. Procédé de préparation d'un composé conforme à la revendication 1, dans lequel R^1 a la signification indiquée dans la revendication 1, excepté celle d'un atome d'hydrogène, lequel procédé comporte une étape de réaction d'un composé de formule



(Ic)

dans laquelle R^2, R^3, X^1 et Y-Z ont les significations indiquées dans la revendication 1,

avec un composé de formule

$$R^{1a}\text{-}L$$

où R^{1a} a la signification donnée ci-dessus pour R^1 et L représente un groupe partant.